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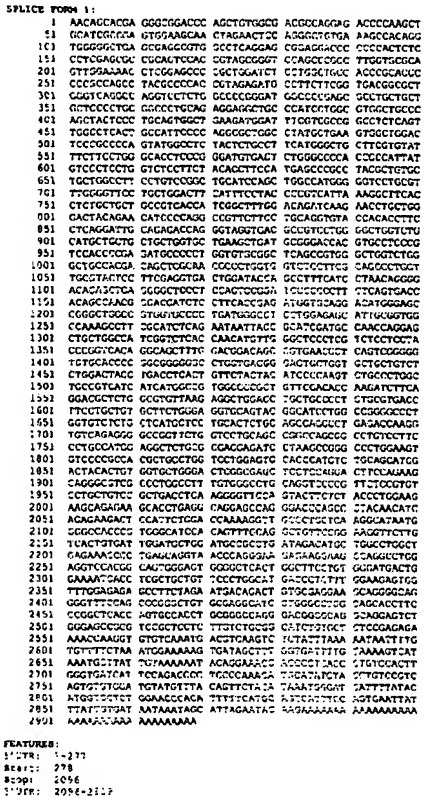
(54) Title: ISOLATED HUMAN TRANSPORTER PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN TRANSPORTER PROTEINS, AND USES THEREOF



(57) Abstract: The present invention provides amino acid sequences acid sequences of peptides that are encoded by genes within the human genome, the transporter peptides of the present invention. The present invention specifically provides isolated peptide adnf nucleic acid molecules, methods of identifying orthlogs and paralogs of of the transporter peptides, and methods of identifying modulators of the transporter peptides.

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ISOLATED HUMAN TRANSPORTER PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN TRANSPORTER PROTEINS, AND USES THEREOF

RELATED APPLICATIONS

The present application is a Continuation-In-Part of U.S. Serial No.09/630,719, filed August 2, 2000 and Continuation-In-Part of U.S. Serial No. 09/765,344.

FIELD OF THE INVENTION

The present invention is in the field of transporter proteins that are related to the sulfate transporter subfamily, recombinant DNA molecules, and protein production. The present invention specifically provides novel peptides and proteins, representing two splice forms of a novel sulfate transporter, that effect ligand transport and nucleic acid molecules encoding such peptide and protein molecules, all of which are useful in the development of human therapeutics and diagnostic compositions and methods.

BACKGROUND OF THE INVENTION

Transporters

Transporter proteins regulate many different functions of a cell, including cell proliferation, differentiation, and signaling processes, by regulating the flow of molecules such as ions and macromolecules, into and out of cells. Transporters are found in the plasma membranes of virtually every cell in eukaryotic organisms. Transporters mediate a variety of cellular functions including regulation of membrane potentials and absorption and secretion of molecules and ion across cell membranes. When present in intracellular membranes of the Golgi apparatus and endocytic vesicles, transporters, such as chloride channels, also regulate organelle pH. For a review, see Greger, R. (1988) Annu. Rev. Physiol. 50:111-122.

Transporters are generally classified by structure and the type of mode of action. In addition, transporters are sometimes classified by the molecule type that is transported, for example, sugar transporters, chlorine channels, potassium channels, etc. There may be many classes of channels for transporting a single type of molecule (a detailed review of channel types can be found at Alexander, S.P.H. and J.A. Peters: Receptor and transporter nomenclature

supplement. Trends Pharmacol. Sci., Elsevier, pp. 65-68 (1997) and http://www-biology.ucsd.edu/~msaier/transport/titlepage2.html.

Ion channels

An important type of transporter is the ion channel. Ion channels regulate many different cell proliferation, differentiation, and signaling processes by regulating the flow of ions into and out of cells. Ion channels are found in the plasma membranes of virtually every cell in eukaryotic organisms. Ion channels mediate a variety of cellular functions including regulation of membrane potentials and absorption and secretion of ion across epithelial membranes. When present in intracellular membranes of the Golgi apparatus and endocytic vesicles, ion channels, such as chloride channels, also regulate organelle pH. For a review, see Greger, R. (1988) Annu. Rev. Physiol. 50:111-122.

Ion channels are generally classified by structure and the type of mode of action. For example, extracellular ligand gated channels (ELGs) are comprised of five polypeptide subunits, with each subunit having 4 membrane spanning domains, and are activated by the binding of an extracellular ligand to the channel. In addition, channels are sometimes classified by the ion type that is transported, for example, chlorine channels, potassium channels, etc. There may be many classes of channels for transporting a single type of ion (a detailed review of channel types can be found at Alexander, S.P.H. and J.A. Peters (1997). Receptor and ion channel nomenclature supplement. Trends Pharmacol. Sci., Elsevier, pp. 65-68 and http://www-biology.ucsd.edu/~msaier/transport/toc.html.

There are many types of ion channels based on structure. For example, many ion channels fall within one of the following groups: extracellular ligand-gated channels (ELG), intracellular ligand-gated channels (ILG), inward rectifying channels (INR), intercellular (gap junction) channels, and voltage gated channels (VIC). There are additionally recognized other channel families based on ion-type transported, cellular location and drug sensitivity. Detailed information on each of these, their activity, ligand type, ion type, disease association, drugability, and other information pertinent to the present invention, is well known in the art.

Anion transport proteins

The present invention provides two splice forms of a novel human anion transport protein that shows a particularly high degree of similarity to sulfate transporters. The alternative splice forms are herein referred to as splice forms 1 and 2. Splice form 1 has been previously disclosed by applicant in U.S. application 09/630,719, filed August 2, 2000.

Anion transport proteins in mammalian cells participate in a wide variety of cell and intracellular organelle functions, including regulation of electrical activity, pH, volume, and the transport of osmolites and metabolites. These proteins also have essential physiological roles in the control of immunological responses, cell migration, cell proliferation, and differentiation. Several classes of anion transporters have been characterized with varying molecular structures and mechanisms for mediating anion flux. One of the most prominent anion transporter super-families is the multiple membrane-spanning permeases, which include Na+- or H+-dependent anion coanion transporters (symporters), anion/anion exchangers (antiporters), and cation-independent anion uniporters. This super-family is also referred to as the Carrier-type anion transporters <http://www-biology.ucsd.edu/~msaier/transport/titlepage2.html>. Typically, proteins within this group contain 8-14 hydrophobic alpha-helical peptide segments that allow the protein to reside in the membrane bilayer. These helices also establish the pathway for ion translocation. Both broad-substrate and substrate-specific anion transporters are known: the former type enables multiple anion species (chloride, iodide, sulfate, bromide, etc.) to permeate the bounding membrane, while anion transporters in the latter class restrict ion movement to one chemical species.

Anion transporter genes and gene products are potential causative agents of disease and disease phenotypes may be actuated both by alterations in gene transcription and by mutations in the protein sequence. For example, the down-regulated in adenoma (DRA) gene was originally identified as a gene that was down-regulated in colon tumors. It encodes a protein with anion transporter function that is expressed in the intestinal tract (duodenum, ileum, cecum, distal colon), but not in the esophagus or stomach (Antalis T.M., Reeder J.A., Gotley D.C. *et al.*, *Clin Cancer Res* (1998) Aug;4(8):1857-63; Byeon M.K., Westerman M.A., Maroulakou I.G. *et al.*, *Oncogene* (1996) Jan 18;12(2):387-96). A second illustration of the biomedical significance of anion transporters is found with patients presenting severe hypothyroidism caused by a congenital lack of iodide transport. These individuals do not accumulate iodide in their thyroids. A single amino acid substitution in the thyroid Na+/I- symporter, where proline replaced threonine at position 354, has been identified as the cause of this condition in two independent patients (Levy O., Ginter C.S., De la Vieja A. *et al.*, *FEBS Lett* (1998) Jun 5;429(1):36-40). Equally compelling are two well-documented autosomal recessive disorders Pendred syndrome and Diastrophic dysplasia (DTD). Pendred syndrome is the most common form of syndromic deafness and characterized by congenital sensorineural hearing loss and goitre. This disorder has been mapped to chromosome 7 and the gene product causing Pendred syndrome (PDS) has been

identified as a anion transporter for iodide and chloride (Scott D.A., Wang R., Kreman T.M. *et al.*, *Nat Genet* (1999)Apr;21(4):440-3). DTD is a well-characterized osteochondrodysplasia with clinical features including dwarfism, spinal deformation, and specific joint abnormalities. The disease occurs in most populations. The gene has been mapped to distal chromosome 5q and it encodes a sulfate anion transporter (Hastbacka J., de la Chapelle A., Mahtani M.M. *et al.*, *Cell* 1994 Sep 23;78(6):1073-87).

Issued US Patents that demonstrate the utility for this group of protein/DNA molecules include, but are not limited to, 6,054,558 "Compositions and methods for the treatment and diagnosis of cardiovascular disease using rchd534 as a target"; 6,048,709 "Compositions and methods for the treatment and diagnosis of cardiovascular disease"; 6,046,030 "Human LIG-1 homolog (HLIG-1)"; 6,025,160 "Polynucleotide and polypeptide sequences encoding rat mdr1b2 and screening methods thereof"; 6 6,013,672 "Agonists of metabotropic glutamate receptors and uses thereof"; 6,008,015 "Glycine transporter"; 5,989,825 "Excitatory amino acid transporter gene and uses"; and 5,928,926 "Isolation and cloning of the human ARSA-I gene and uses thereof".

Transporter proteins, particularly members of the sulfate transporter subfamily, are a major target for drug action and development, particularly members that are expressed in the tissue types noted in Figure 1 (e.g. neoplastic cells)). Accordingly, it is valuable to the field of pharmaceutical development to identify and characterize previously unknown transport proteins. The present invention advances the state of the art by providing a previously unidentified human transport protein.

SUMMARY OF THE INVENTION

The present invention is based in part on the identification of amino acid sequences of human transporter peptides and proteins that are related to the sulfate transporter subfamily, as well as allelic variants and other mammalian orthologs thereof. Specifically, the present invention provides two splice forms of a novel human sulfate transporter protein. These unique peptide sequences, and nucleic acid sequences that encode these peptides, can be used as models for the development of human therapeutic targets, aid in the identification of therapeutic proteins, and serve as targets for the development of human therapeutic agents that modulate transporter activity in cells and tissues that express the transporter. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal

muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas.

DESCRIPTION OF THE FIGURE SHEETS

FIGURE 1 provides the nucleotide sequences of cDNA molecules that encode splice forms 1 and 2 of the transporter protein of the present invention (splice form 1 = SEQ ID NO:1, splice form 2 = SEQ ID NO:4). In addition, structure and functional information is provided, such as ATG start, stop and tissue distribution, where available, that allows one to readily determine specific uses of the inventions based on these molecular sequences. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas.

FIGURE 2 provides the predicted amino acid sequences of splice forms 1 and 2 of the transporter of the present invention (splice form 1 = SEQ ID NO:2, splice form 2 = SEQ ID NO:5). In addition, structure and functional information such as protein family, function, and modification sites is provided where available, allowing one to readily determine specific uses of the inventions based on these molecular sequences.

FIGURE 3 provides a genomic sequence SEQ ID NO:3) that spans the gene encoding splice forms 1 and 2 of the transporter protein of the present invention. In addition, structure and functional information, such as intron/exon structure, promoter location, etc., is provided where available, allowing one to readily determine specific uses of the inventions based on this molecular sequence. As illustrated in Figure 3, identified SNP variations include g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t. Figure 3 also provides structural information for splice form 2, derived from the Genewise computer program.

DETAILED DESCRIPTION OF THE INVENTION

General Description

The present invention is based on the sequencing of the human genome. During the sequencing and assembly of the human genome, analysis of the sequence information revealed previously unidentified fragments of the human genome that encode peptides that share structural and/or sequence homology to protein/peptide/domains identified and characterized within the art as being a transporter protein or part of a transporter protein and are related to the sulfate transporter subfamily. Specifically, the present invention provides two splice forms of a novel human sulfate transporter. Utilizing these sequences, additional genomic sequences were assembled and transcript and/or cDNA sequences were isolated and characterized. Based on this analysis, the present invention provides amino acid sequences of human transporter peptides and proteins that are related to the sulfate transporter subfamily, nucleic acid sequences in the form of transcript sequences, cDNA sequences and/or genomic sequences that encode these transporter peptides and proteins, nucleic acid variation (allelic information), tissue distribution of expression, and information about the closest art known protein/peptide/domain that has structural or sequence homology to the transporter of the present invention.

In addition to being previously unknown, the peptides that are provided in the present invention are selected based on their ability to be used for the development of commercially important products and services. Specifically, the present peptides are selected based on homology and/or structural relatedness to known transporter proteins of the sulfate transporter subfamily and the expression pattern observed. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas.. The art has clearly established the commercial importance of members of this family of proteins and proteins that have expression patterns similar to that of the present gene. Some of the more specific features of the peptides of the present invention, and the uses thereof, are described herein, particularly in the Background of the Invention and in the annotation provided in the Figures, and/or are known within the art for each of the known sulfate transporter family or subfamily of transporter proteins.

Specific Embodiments

Peptide Molecules

The present invention provides nucleic acid sequences that encode protein molecules that have been identified as being members of the transporter family of proteins and are related to the sulfate transporter subfamily (protein sequences are provided in Figure 2, cDNA sequences are provided in Figures 1 and genomic sequences are provided in Figure 3). Specifically, the present invention provides two splice forms of a novel human sulfate transporter. The peptide sequences provided in Figure 2, as well as the obvious variants described herein, particularly allelic variants as identified herein and using the information in Figure 3, will be referred herein as the transporter peptides of the present invention, transporter peptides, or peptides/proteins of the present invention.

The present invention provides isolated peptide and protein molecules that consist of, consist essentially of, or comprising the amino acid sequences of the transporter peptides disclosed in the Figure 2, (encoded by the nucleic acid molecule shown in Figure 1, transcript/cDNA or Figure 3, genomic sequence), as well as all obvious variants of these peptides that are within the art to make and use. Some of these variants are described in detail below.

As used herein, a peptide is said to be "isolated" or "purified" when it is substantially free of cellular material or free of chemical precursors or other chemicals. The peptides of the present invention can be purified to homogeneity or other degrees of purity. The level of purification will be based on the intended use. The critical feature is that the preparation allows for the desired function of the peptide, even if in the presence of considerable amounts of other components (the features of an isolated nucleic acid molecule is discussed below).

In some uses, "substantially free of cellular material" includes preparations of the peptide having less than about 30% (by dry weight) other proteins (i.e., contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins. When the peptide is recombinantly produced, it can also be substantially free of culture medium, i.e., culture medium represents less than about 20% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of the peptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical

precursors or other chemicals" includes preparations of the transporter peptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

The isolated transporter peptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. For example, a nucleic acid molecule encoding the transporter peptide is cloned into an expression vector, the expression vector introduced into a host cell and the protein expressed in the host cell. The protein can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques. Many of these techniques are described in detail below.

Accordingly, the present invention provides proteins that consist of the amino acid sequences provided in Figure 2 (SEQ ID NOS:2 and 5), for example, proteins encoded by the cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NOS:1 and 4) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). The amino acid sequence of such a protein is provided in Figure 2. A protein consists of an amino acid sequence when the amino acid sequence is the final amino acid sequence of the protein.

The present invention further provides proteins that consist essentially of the amino acid sequences provided in Figure 2 (SEQ ID NOS:2 and 5), for example, proteins encoded by the cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NOS:1 and 4) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). A protein consists essentially of an amino acid sequence when such an amino acid sequence is present with only a few additional amino acid residues, for example from about 1 to about 100 or so additional residues, typically from 1 to about 20 additional residues in the final protein.

The present invention further provides proteins that comprise the amino acid sequences provided in Figure 2 (SEQ ID NOS:2 and 5), for example, proteins encoded by the cDNA nucleic acid sequences shown in Figure 1 (SEQ ID NOS:1 and 4) and the genomic sequences provided in Figure 3 (SEQ ID NO:3). A protein comprises an amino acid sequence when the amino acid

sequence is at least part of the final amino acid sequence of the protein. In such a fashion, the protein can be only the peptide or have additional amino acid molecules, such as amino acid residues (contiguous encoded sequence) that are naturally associated with it or heterologous amino acid residues/peptide sequences. Such a protein can have a few additional amino acid residues or can comprise several hundred or more additional amino acids. The preferred classes of proteins that are comprised of the transporter peptides of the present invention are the naturally occurring mature proteins. A brief description of how various types of these proteins can be made/isolated is provided below.

The transporter peptides of the present invention can be attached to heterologous sequences to form chimeric or fusion proteins. Such chimeric and fusion proteins comprise a transporter peptide operatively linked to a heterologous protein having an amino acid sequence not substantially homologous to the transporter peptide. "Operatively linked" indicates that the transporter peptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the transporter peptide.

In some uses, the fusion protein does not affect the activity of the transporter peptide *per se*. For example, the fusion protein can include, but is not limited to, enzymatic fusion proteins, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, MYC-tagged, HI-tagged and Ig fusions. Such fusion proteins, particularly poly-His fusions, can facilitate the purification of recombinant transporter peptide. In certain host cells (e.g., mammalian host cells), expression and/or secretion of a protein can be increased by using a heterologous signal sequence.

A chimeric or fusion protein can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different protein sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST protein). A transporter peptide-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the transporter peptide.

As mentioned above, the present invention also provides and enables obvious variants of the amino acid sequence of the proteins of the present invention, such as naturally occurring mature

forms of the peptide, allelic/sequence variants of the peptides, non-naturally occurring recombinantly derived variants of the peptides, and orthologs and paralogs of the peptides. Such variants can readily be generated using art-known techniques in the fields of recombinant nucleic acid technology and protein biochemistry. It is understood, however, that variants exclude any amino acid sequences disclosed prior to the invention.

Such variants can readily be identified/made using molecular techniques and the sequence information disclosed herein. Further, such variants can readily be distinguished from other peptides based on sequence and/or structural homology to the transporter peptides of the present invention. The degree of homology/identity present will be based primarily on whether the peptide is a functional variant or non-functional variant, the amount of divergence present in the paralog family and the evolutionary distance between the orthologs.

To determine the percent identity of two amino acid sequences or two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, at least 30%, 40%, 50%, 60%, 70%, 80%, or 90% or more of a reference sequence is aligned for comparison purposes. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity and similarity between two sequences can be accomplished using a mathematical algorithm. (*Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part 1*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm

which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux, J., *et al., Nucleic Acids Res. 12(1)*:387 (1984)) (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the algorithm of E. Myers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against sequence databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (*J. Mol. Biol.* 215:403-10 (1990)). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (*Nucleic Acids Res.* 25(17):3389-3402 (1997)). When utilizing BLAST and gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

Full-length pre-processed forms, as well as mature processed forms, of proteins that comprise one of the peptides of the present invention can readily be identified as having complete sequence identity to one of the transporter peptides of the present invention as well as being encoded by the same genetic locus as the transporter peptide provided herein. RH panel mapping shows the gene encoding the transporter proteins of the present invention is found on chromosome 17 near markers SHGC-56719 and SHGC-58932 (LOD=15.9 and 15.68).

Allelic variants of a transporter peptide can readily be identified as being a human protein having a high degree (significant) of sequence homology/identity to at least a portion of the transporter peptide as well as being encoded by the same genetic locus as the transporter peptide provided herein. Genetic locus can readily be determined based on the genomic information

provided in Figure 3, such as the genomic sequence mapped to the reference human. RH panel mapping shows the gene encoding the transporter proteins of the present invention is found on chromosome 17 near markers SHGC-56719 and SHGC-58932 (LOD=15.9 and 15.68). As used herein, two proteins (or a region of the proteins) have significant homology when the amino acid sequences are typically at least about 70-80%, 80-90%, and more typically at least about 90-95% or more homologous. A significantly homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid sequence that will hybridize to a transporter peptide encoding nucleic acid molecule under stringent conditions as more fully described below.

Figure 3 provides information on SNPs that have been found in the gene encoding the transporter proteins of the present invention. The following variations were seen: g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t.

Paralogs of a transporter peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the transporter peptide, as being encoded by a gene from humans, and as having similar activity or function. Two proteins will typically be considered paralogs when the amino acid sequences are typically at least about 60% or greater, and more typically at least about 70% or greater homology through a given region or domain. Such paralogs will be encoded by a nucleic acid sequence that will hybridize to a transporter peptide encoding nucleic acid molecule under moderate to stringent conditions as more fully described below.

Orthologs of a transporter peptide can readily be identified as having some degree of significant sequence homology/identity to at least a portion of the transporter peptide as well as being encoded by a gene from another organism. Preferred orthologs will be isolated from mammals, preferably primates, for the development of human therapeutic targets and agents. Such orthologs will be encoded by a nucleic acid sequence that will hybridize to a transporter peptide encoding nucleic acid molecule under moderate to stringent conditions, as more fully described below, depending on the degree of relatedness of the two organisms yielding the proteins.

Non-naturally occurring variants of the transporter peptides of the present invention can readily be generated using recombinant techniques. Such variants include, but are not limited to deletions, additions and substitutions in the amino acid sequence of the transporter peptide. For example, one class of substitutions are conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a transporter peptide by another amino acid of like

characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu; substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science 247*:1306-1310 (1990).

Variant transporter peptides can be fully functional or can lack function in one or more activities, e.g. ability to bind ligand, ability to transport ligand, ability to mediate signaling, etc. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Figure 2 provides the result of protein analysis and can be used to identify critical domains/regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree.

Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science 244*:1081-1085 (1989)), particularly using the results provided in Figure 2. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as transporter activity or in assays such as an *in vitro* proliferative activity. Sites that are critical for binding partner/substrate binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol. 224*:899-904 (1992); de Vos *et al. Science 255*:306-312 (1992)).

The present invention further provides fragments of the transporter peptides, in addition to proteins and peptides that comprise and consist of such fragments, particularly those comprising the residues identified in Figure 2. The fragments to which the invention pertains, however, are not to be construed as encompassing fragments that may be disclosed publicly prior to the present invention.

As used herein, a fragment comprises at least 8, 10, 12, 14, 16, or more contiguous amino acid residues from a transporter peptide. Such fragments can be chosen based on the ability to retain one or more of the biological activities of the transporter peptide or could be chosen for the

ability to perform a function, e.g. bind a substrate or act as an immunogen. Particularly important fragments are biologically active fragments, peptides that are, for example, about 8 or more amino acids in length. Such fragments will typically comprise a domain or motif of the transporter peptide, e.g., active site, a transmembrane domain or a substrate-binding domain. Further, possible fragments include, but are not limited to, domain or motif containing fragments, soluble peptide fragments, and fragments containing immunogenic structures. Predicted domains and functional sites are readily identifiable by computer programs well known and readily available to those of skill in the art (e.g., PROSITE analysis). The results of one such analysis are provided in Figure 2.

Polypeptides often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids. Further, many amino acids, including the terminal amino acids, may be modified by natural processes, such as processing and other post-translational modifications, or by chemical modification techniques well known in the art. Common modifications that occur naturally in transporter peptides are described in basic texts, detailed monographs, and the research literature, and they are well known to those of skill in the art (some of these features are identified in Figure 2).

Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cystine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

Such modifications are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins - Structure and Molecular Properties*, 2nd Ed., T.E. Creighton, W. H. Freeman and Company, New York (1993). Many detailed reviews are available on this subject, such as by Wold, F., *Posttranslational Covalent Modification of Proteins*, B.C. Johnson, Ed., Academic Press, New York 1-12 (1983); Seifter *et al.* (*Meth. Enzymol. 182*: 626-646 (1990)) and Rattan *et al.* (*Ann. N.Y. Acad. Sci. 663*:48-62 (1992)).

Accordingly, the transporter peptides of the present invention also encompass derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code, in which a substituent group is included, in which the mature transporter peptide is fused with another compound, such as a compound to increase the half-life of the transporter peptide (for example, polyethylene glycol), or in which the additional amino acids are fused to the mature transporter peptide, such as a leader or secretory sequence or a sequence for purification of the mature transporter peptide or a pro-protein sequence.

Protein/Peptide Uses

The proteins of the present invention can be used in substantial and specific assays related to the functional information provided in the Figures; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its binding partner or ligand) in biological fluids; and as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state). Where the protein binds or potentially binds to another protein or ligand (such as, for example, in a transporter-effector protein interaction or transporter-ligand interaction), the protein can be used to identify the binding partner/ligand so as to develop a system to identify inhibitors of the binding interaction. Any or all of these uses are capable of being developed into reagent grade or kit format for commercialization as commercial products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

The potential uses of the peptides of the present invention are based primarily on the source of the protein as well as the class/action of the protein. For example, transporters isolated from humans and their human/mammalian orthologs serve as targets for identifying agents for use in mammalian therapeutic applications, e.g. a human drug, particularly in modulating a biological or pathological response in a cell or tissue that expresses the transporter. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas.

Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen. A large percentage of pharmaceutical agents are being developed that modulate the activity of transporter proteins, particularly members of the sulfate transporter subfamily (see Background of the Invention). The structural and functional information provided in the Background and Figures provide specific and substantial uses for the molecules of the present invention, particularly in combination with the expression information provided in Figure 1. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. Such uses can readily be determined using the information provided herein, that known in the art and routine experimentation.

The proteins of the present invention (including variants and fragments that may have been disclosed prior to the present invention) are useful for biological assays related to transporters that are related to members of the sulfate transporter subfamily. Such assays involve any of the known transporter functions or activities or properties useful for diagnosis and treatment of transporter-related conditions that are specific for the subfamily of transporters that the one of the present invention belongs to, particularly in cells and tissues that express the transporter. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen. The proteins of the present invention are also useful in drug screening assays, in cell-based or cell-free systems ((Hodgson, Bio/technology, 1992, Sept 10(9);973-80). Cell-based systems can be native, i.e., cells that normally express the transporter, as a biopsy or expanded in cell culture. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated

tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. In an alternate embodiment, cell-based assays involve recombinant host cells expressing the transporter protein.

The polypeptides can be used to identify compounds that modulate transporter activity of the protein in its natural state or an altered form that causes a specific disease or pathology associated with the transporter. Both the transporters of the present invention and appropriate variants and fragments can be used in high-throughput screens to assay candidate compounds for the ability to bind to the transporter. These compounds can be further screened against a functional transporter to determine the effect of the compound on the transporter activity. Further, these compounds can be tested in animal or invertebrate systems to determine activity/effectiveness. Compounds can be identified that activate (agonist) or inactivate (antagonist) the transporter to a desired degree.

Further, the proteins of the present invention can be used to screen a compound for the ability to stimulate or inhibit interaction between the transporter protein and a molecule that normally interacts with the transporter protein, e.g. a substrate or a component of the signal pathway that the transporter protein normally interacts (for example, another transporter). Such assays typically include the steps of combining the transporter protein with a candidate compound under conditions that allow the transporter protein, or fragment, to interact with the target molecule, and to detect the formation of a complex between the protein and the target or to detect the biochemical consequence of the interaction with the transporter protein and the target, such as any of the associated effects of signal transduction such as changes in membrane potential, protein phosphorylation, cAMP turnover, and adenylate cyclase activation, etc.

Candidate compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, e.g., Lam *et al.*, *Nature 354*:82-84 (1991); Houghten *et al.*, *Nature 354*:84-86 (1991)) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (e.g., members of random and partially degenerate, directed phosphopeptide libraries, see, e.g., Songyang *et al.*, *Cell 72*:767-778 (1993)); 3) antibodies (e.g., polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, $F(ab')_2$, Fab expression library

fragments, and epitope-binding fragments of antibodies); and 4) small organic and inorganic molecules (e.g., molecules obtained from combinatorial and natural product libraries).

One candidate compound is a soluble fragment of the receptor that competes for ligand binding. Other candidate compounds include mutant transporters or appropriate fragments containing mutations that affect transporter function and thus compete for ligand. Accordingly, a fragment that competes for ligand, for example with a higher affinity, or a fragment that binds ligand but does not allow release, is encompassed by the invention.

The invention further includes other end point assays to identify compounds that modulate (stimulate or inhibit) transporter activity. The assays typically involve an assay of events in the signal transduction pathway that indicate transporter activity. Thus, the transport of a ligand, change in cell membrane potential, activation of a protein, a change in the expression of genes that are up- or down-regulated in response to the transporter protein dependent signal cascade can be assayed.

Any of the biological or biochemical functions mediated by the transporter can be used as an endpoint assay. These include all of the biochemical or biochemical/biological events described herein, in the references cited herein, incorporated by reference for these endpoint assay targets, and other functions known to those of ordinary skill in the art or that can be readily identified using the information provided in the Figures, particularly Figure 2. Specifically, a biological function of a cell or tissues that expresses the transporter can be assayed. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen.

Binding and/or activating compounds can also be screened by using chimeric transporter proteins in which the amino terminal extracellular domain, or parts thereof, the entire transmembrane domain or subregions, such as any of the seven transmembrane segments or any of the intracellular or extracellular loops and the carboxy terminal intracellular domain, or parts thereof, can be replaced by heterologous domains or subregions. For example, a ligand-binding region can be used that interacts with a different ligand then that which is recognized by the native transporter. Accordingly, a different set of signal transduction components is available as an end-

point assay for activation. This allows for assays to be performed in other than the specific host cell from which the transporter is derived.

The proteins of the present invention are also useful in competition binding assays in methods designed to discover compounds that interact with the transporter (e.g. binding partners and/or ligands). Thus, a compound is exposed to a transporter polypeptide under conditions that allow the compound to bind or to otherwise interact with the polypeptide. Soluble transporter polypeptide is also added to the mixture. If the test compound interacts with the soluble transporter polypeptide, it decreases the amount of complex formed or activity from the transporter target. This type of assay is particularly useful in cases in which compounds are sought that interact with specific regions of the transporter. Thus, the soluble polypeptide that competes with the target transporter region is designed to contain peptide sequences corresponding to the region of interest.

To perform cell free drug screening assays, it is sometimes desirable to immobilize either the transporter protein, or fragment, or its target molecule to facilitate separation of complexes from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay.

Techniques for immobilizing proteins on matrices can be used in the drug screening assays. In one embodiment, a fusion protein can be provided which adds a domain that allows the protein to be bound to a matrix. For example, glutathione-S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the cell lysates (e.g., ^{35}S-labeled) and the candidate compound, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads are washed to remove any unbound label, and the matrix immobilized and radiolabel determined directly, or in the supernatant after the complexes are dissociated. Alternatively, the complexes can be dissociated from the matrix, separated by SDS-PAGE, and the level of transporter-binding protein found in the bead fraction quantitated from the gel using standard electrophoretic techniques. For example, either the polypeptide or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin using techniques well known in the art. Alternatively, antibodies reactive with the protein but which do not interfere with binding of the protein to its target molecule can be derivatized to the wells of the plate, and the protein trapped in the wells by antibody conjugation. Preparations of a transporter-binding protein and a candidate compound are incubated in the transporter protein-presenting wells and the amount of complex trapped in the well can be quantitated. Methods for detecting such complexes, in addition to those described above for the

GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the transporter protein target molecule, or which are reactive with transporter protein and compete with the target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the target molecule.

Agents that modulate one of the transporters of the present invention can be identified using one or more of the above assays, alone or in combination. It is generally preferable to use a cell-based or cell free system first and then confirm activity in an animal or other model system. Such model systems are well known in the art and can readily be employed in this context.

Modulators of transporter protein activity identified according to these drug screening assays can be used to treat a subject with a disorder mediated by the transporter pathway, by treating cells or tissues that express the transporter. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. These methods of treatment include the steps of administering a modulator of transporter activity in a pharmaceutical composition to a subject in need of such treatment, the modulator being identified as described herein.

In yet another aspect of the invention, the transporter proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with the transporter and are involved in transporter activity. Such transporter-binding proteins are also likely to be involved in the propagation of signals by the transporter proteins or transporter targets as, for example, downstream elements of a transporter-mediated signaling pathway. Alternatively, such transporter-binding proteins are likely to be transporter inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a transporter protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an

unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo,* forming a transporter-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the transporter protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a transporter-modulating agent, an antisense transporter nucleic acid molecule, a transporter-specific antibody, or a transporter-binding partner) can be used in an animal or other model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal or other model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

The transporter proteins of the present invention are also useful to provide a target for diagnosing a disease or predisposition to disease mediated by the peptide. Accordingly, the invention provides methods for detecting the presence, or levels of, the protein (or encoding mRNA) in a cell, tissue, or organism. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. The method involves contacting a biological sample with a compound capable of interacting with the transporter protein such that the interaction can be detected. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

One agent for detecting a protein in a sample is an antibody capable of selectively binding to protein. A biological sample includes tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject.

The peptides of the present invention also provide targets for diagnosing active protein activity, disease, or predisposition to disease, in a patient having a variant peptide, particularly activities and conditions that are known for other members of the family of proteins to which the present one belongs. Thus, the peptide can be isolated from a biological sample and assayed for the presence of a genetic mutation that results in aberrant peptide. This includes amino acid substitution, deletion, insertion, rearrangement, (as the result of aberrant splicing events), and inappropriate post-translational modification. Analytic methods include altered electrophoretic mobility, altered tryptic peptide digest, altered transporter activity in cell-based or cell-free assay, alteration in ligand or antibody-binding pattern, altered isoelectric point, direct amino acid sequencing, and any other of the known assay techniques useful for detecting mutations in a protein. Such an assay can be provided in a single detection format or a multi-detection format such as an antibody chip array.

In vitro techniques for detection of peptide include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence using a detection reagent, such as an antibody or protein binding agent. Alternatively, the peptide can be detected *in vivo* in a subject by introducing into the subject a labeled anti-peptide antibody or other types of detection agent. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. Particularly useful are methods that detect the allelic variant of a peptide expressed in a subject and methods which detect fragments of a peptide in a sample.

The peptides are also useful in pharmacogenomic analysis. Pharmacogenomics deal with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, e.g., Eichelbaum, M. (*Clin. Exp. Pharmacol. Physiol.* 23(10-11):983-985 (1996)), and Linder, M.W. (*Clin. Chem.* 43(2):254-266 (1997)). The clinical outcomes of these variations result in severe toxicity of therapeutic drugs in certain individuals or therapeutic failure of drugs in certain individuals as a result of individual variation in metabolism. Thus, the genotype of the individual can determine the way a therapeutic compound acts on the body or the way the body metabolizes the compound. Further, the activity of drug metabolizing enzymes effects both the intensity and duration of drug action. Thus, the pharmacogenomics of the individual permit the selection of effective compounds and effective dosages of such compounds for prophylactic or therapeutic treatment based on the individual's genotype. The discovery of genetic polymorphisms in some drug metabolizing enzymes has explained why some patients do not obtain the expected drug effects, show an exaggerated drug effect, or experience serious toxicity from

standard drug dosages. Polymorphisms can be expressed in the phenotype of the extensive metabolizer and the phenotype of the poor metabolizer. Accordingly, genetic polymorphism may lead to allelic protein variants of the transporter protein in which one or more of the transporter functions in one population is different from those in another population. The peptides thus allow a target to ascertain a genetic predisposition that can affect treatment modality. Thus, in a ligand-based treatment, polymorphism may give rise to amino terminal extracellular domains and/or other ligand-binding regions that are more or less active in ligand binding, and transporter activation. Accordingly, ligand dosage would necessarily be modified to maximize the therapeutic effect within a given population containing a polymorphism. As an alternative to genotyping, specific polymorphic peptides could be identified.

The peptides are also useful for treating a disorder characterized by an absence of, inappropriate, or unwanted expression of the protein. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. Accordingly, methods for treatment include the use of the transporter protein or fragments.

Antibodies

The invention also provides antibodies that selectively bind to one of the peptides of the present invention, a protein comprising such a peptide, as well as variants and fragments thereof. As used herein, an antibody selectively binds a target peptide when it binds the target peptide and does not significantly bind to unrelated proteins. An antibody is still considered to selectively bind a peptide even if it also binds to other proteins that are not substantially homologous with the target peptide so long as such proteins share homology with a fragment or domain of the peptide target of the antibody. In this case, it would be understood that antibody binding to the peptide is still selective despite some degree of cross-reactivity.

As used herein, an antibody is defined in terms consistent with that recognized within the art: they are multi-subunit proteins produced by a mammalian organism in response to an antigen challenge. The antibodies of the present invention include polyclonal antibodies and monoclonal antibodies, as well as fragments of such antibodies, including, but not limited to, Fab or $F(ab')_2$, and Fv fragments.

Many methods are known for generating and/or identifying antibodies to a given target peptide. Several such methods are described by Harlow, Antibodies, Cold Spring Harbor Press, (1989).

In general, to generate antibodies, an isolated peptide is used as an immunogen and is administered to a mammalian organism, such as a rat, rabbit or mouse. The full-length protein, an antigenic peptide fragment or a fusion protein can be used. Particularly important fragments are those covering functional domains, such as the domains identified in Figure 2, and domain of sequence homology or divergence amongst the family, such as those that can readily be identified using protein alignment methods and as presented in the Figures.

Antibodies are preferably prepared from regions or discrete fragments of the transporter proteins. Antibodies can be prepared from any region of the peptide as described herein. However, preferred regions will include those involved in function/activity and/or transporter/binding partner interaction. Figure 2 can be used to identify particularly important regions while sequence alignment can be used to identify conserved and unique sequence fragments.

An antigenic fragment will typically comprise at least 8 contiguous amino acid residues. The antigenic peptide can comprise, however, at least 10, 12, 14, 16 or more amino acid residues. Such fragments can be selected on a physical property, such as fragments correspond to regions that are located on the surface of the protein, e.g., hydrophilic regions or can be selected based on sequence uniqueness (see Figure 2).

Detection on an antibody of the present invention can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Antibody Uses

The antibodies can be used to isolate one of the proteins of the present invention by standard techniques, such as affinity chromatography or immunoprecipitation. The antibodies can facilitate the purification of the natural protein from cells and recombinantly produced protein expressed in host cells. In addition, such antibodies are useful to detect the presence of one of the proteins of the present invention in cells or tissues to determine the pattern of expression of the protein among various tissues in an organism and over the course of normal development. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen. Further, such antibodies can be used to detect protein *in situ*, *in vitro*, or in a cell lysate or supernatant in order to evaluate the abundance and pattern of expression. Also, such antibodies can be used to assess abnormal tissue distribution or abnormal expression during development or progression of a biological condition. Antibody detection of circulating fragments of the full length protein can be used to identify turnover.

Further, the antibodies can be used to assess expression in disease states such as in active stages of the disease or in an individual with a predisposition toward disease related to the protein's function. When a disorder is caused by an inappropriate tissue distribution, developmental expression, level of expression of the protein, or expressed/processed form, the antibody can be prepared against the normal protein. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. If a disorder is characterized by a specific mutation in the protein, antibodies specific for this mutant protein can be used to assay for the presence of the specific mutant protein.

The antibodies can also be used to assess normal and aberrant subcellular localization of cells in the various tissues in an organism. Independent lines of evidence show expression of splice

form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. The diagnostic uses can be applied, not only in genetic testing, but also in monitoring a treatment modality. Accordingly, where treatment is ultimately aimed at correcting expression level or the presence of aberrant sequence and aberrant tissue distribution or developmental expression, antibodies directed against the protein or relevant fragments can be used to monitor therapeutic efficacy.

Additionally, antibodies are useful in pharmacogenomic analysis. Thus, antibodies prepared against polymorphic proteins can be used to identify individuals that require modified treatment modalities. The antibodies are also useful as diagnostic tools as an immunological marker for aberrant protein analyzed by electrophoretic mobility, isoelectric point, tryptic peptide digest, and other physical assays known to those in the art.

The antibodies are also useful for tissue typing. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. Thus, where a specific protein has been correlated with expression in a specific tissue, antibodies that are specific for this protein can be used to identify a tissue type.

The antibodies are also useful for inhibiting protein function, for example, blocking the binding of the transporter peptide to a binding partner such as a ligand or protein binding partner. These uses can also be applied in a therapeutic context in which treatment involves inhibiting the protein's function. An antibody can be used, for example, to block binding, thus modulating (agonizing or antagonizing) the peptides activity. Antibodies can be prepared against specific fragments containing sites required for function or against intact protein that is associated with a cell or cell membrane. See Figure 2 for structural information relating to the proteins of the present invention.

The invention also encompasses kits for using antibodies to detect the presence of a protein in a biological sample. The kit can comprise antibodies such as a labeled or labelable antibody and a compound or agent for detecting protein in a biological sample; means for determining the amount

of protein in the sample; means for comparing the amount of protein in the sample with a standard; and instructions for use. Such a kit can be supplied to detect a single protein or epitope or can be configured to detect one of a multitude of epitopes, such as in an antibody detection array. Arrays are described in detail below for nucleic acid arrays and similar methods have been developed for antibody arrays.

Nucleic Acid Molecules

The present invention further provides isolated nucleic acid molecules that encode a transporter peptide or protein of the present invention (cDNA, transcript and genomic sequence). Such nucleic acid molecules will consist of, consist essentially of, or comprise a nucleotide sequence that encodes one of the transporter peptides of the present invention, an allelic variant thereof, or an ortholog or paralog thereof.

As used herein, an "isolated" nucleic acid molecule is one that is separated from other nucleic acid present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences that naturally flank the nucleic acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. However, there can be some flanking nucleotide sequences, for example up to about 5KB, 4KB, 3KB, 2KB, or 1KB or less, particularly contiguous peptide encoding sequences and peptide encoding sequences within the same gene but separated by introns in the genomic sequence. The important point is that the nucleic acid is isolated from remote and unimportant flanking sequences such that it can be subjected to the specific manipulations described herein such as recombinant expression, preparation of probes and primers, and other uses specific to the nucleic acid sequences.

Moreover, an "isolated" nucleic acid molecule, such as a transcript/cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. However, the nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated.

For example, recombinant DNA molecules contained in a vector are considered isolated. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the isolated DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Accordingly, the present invention provides nucleic acid molecules that consist of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NOS:1 and 4, cDNA/transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NOS:2 and 5. A nucleic acid molecule consists of a nucleotide sequence when the nucleotide sequence is the complete nucleotide sequence of the nucleic acid molecule.

The present invention further provides nucleic acid molecules that consist essentially of the nucleotide sequence shown in Figure 1 or 3 (SEQ ID NOS:1 and 4, cDNA/transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NOS:2 and 5. A nucleic acid molecule consists essentially of a nucleotide sequence when such a nucleotide sequence is present with only a few additional nucleic acid residues in the final nucleic acid molecule.

The present invention further provides nucleic acid molecules that comprise the nucleotide sequences shown in Figure 1 or 3 (SEQ ID NOS:1 and 4, cDNA/transcript sequence and SEQ ID NO:3, genomic sequence), or any nucleic acid molecule that encodes the protein provided in Figure 2, SEQ ID NOS:2 and 5. A nucleic acid molecule comprises a nucleotide sequence when the nucleotide sequence is at least part of the final nucleotide sequence of the nucleic acid molecule. In such a fashion, the nucleic acid molecule can be only the nucleotide sequence or have additional nucleic acid residues, such as nucleic acid residues that are naturally associated with it or heterologous nucleotide sequences. Such a nucleic acid molecule can have a few additional nucleotides or can comprise several hundred or more additional nucleotides. A brief description of how various types of these nucleic acid molecules can be readily made/isolated is provided below.

In Figures 1 and 3, both coding and non-coding sequences are provided. Because of the source of the present invention, humans genomic sequence (Figure 3) and cDNA/transcript sequences (Figure 1), the nucleic acid molecules in the Figures will contain genomic intronic sequences, 5' and 3' non-coding sequences, gene regulatory regions and non-coding intergenic sequences. In general such sequence features are either noted in Figures 1 and 3 or can readily be identified using computational tools known in the art. As discussed below, some of the non-coding regions, particularly gene regulatory elements such as promoters, are useful for a variety of purposes, e.g. control of heterologous gene expression, target for identifying gene activity modulating compounds, and are particularly claimed as fragments of the genomic sequence provided herein.

The isolated nucleic acid molecules can encode the mature protein plus additional amino or carboxyl-terminal amino acids, or amino acids interior to the mature peptide (when the mature form

has more than one peptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, facilitate protein trafficking, prolong or shorten protein half-life or facilitate manipulation of a protein for assay or production, among other things. As generally is the case *in situ*, the additional amino acids may be processed away from the mature protein by cellular enzymes.

As mentioned above, the isolated nucleic acid molecules include, but are not limited to, the sequence encoding the transporter peptide alone, the sequence encoding the mature peptide and additional coding sequences, such as a leader or secretory sequence (e.g., a pre-pro or pro-protein sequence), the sequence encoding the mature peptide, with or without the additional coding sequences, plus additional non-coding sequences, for example introns and non-coding 5' and 3' sequences such as transcribed but non-translated sequences that play a role in transcription, mRNA processing (including splicing and polyadenylation signals), ribosome binding and stability of mRNA. In addition, the nucleic acid molecule may be fused to a marker sequence encoding, for example, a peptide that facilitates purification.

Isolated nucleic acid molecules can be in the form of RNA, such as mRNA, or in the form DNA, including cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The nucleic acid, especially DNA, can be double-stranded or single-stranded. Single-stranded nucleic acid can be the coding strand (sense strand) or the non-coding strand (anti-sense strand).

The invention further provides nucleic acid molecules that encode fragments of the peptides of the present invention as well as nucleic acid molecules that encode obvious variants of the transporter proteins of the present invention that are described above. Such nucleic acid molecules may be naturally occurring, such as allelic variants (same locus), paralogs (different locus), and orthologs (different organism), or may be constructed by recombinant DNA methods or by chemical synthesis. Such non-naturally occurring variants may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells, or organisms. Accordingly, as discussed above, the variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions.

The present invention further provides non-coding fragments of the nucleic acid molecules provided in Figures 1 and 3. Preferred non-coding fragments include, but are not limited to, promoter sequences, enhancer sequences, gene modulating sequences and gene termination sequences. Such fragments are useful in controlling heterologous gene expression and in

developing screens to identify gene-modulating agents. A promoter can readily be identified as being 5' to the ATG start site in the genomic sequence provided in Figure 3.

A fragment comprises a contiguous nucleotide sequence greater than 12 or more nucleotides. Further, a fragment could at least 30, 40, 50, 100, 250 or 500 nucleotides in length. The length of the fragment will be based on its intended use. For example, the fragment can encode epitope bearing regions of the peptide, or can be useful as DNA probes and primers. Such fragments can be isolated using the known nucleotide sequence to synthesize an oligonucleotide probe. A labeled probe can then be used to screen a cDNA library, genomic DNA library, or mRNA to isolate nucleic acid corresponding to the coding region. Further, primers can be used in PCR reactions to clone specific regions of gene.

A probe/primer typically comprises substantially a purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides.

Orthologs, homologs, and allelic variants can be identified using methods well known in the art. As described in the Peptide Section, these variants comprise a nucleotide sequence encoding a peptide that is typically 60-70%, 70-80%, 80-90%, and more typically at least about 90-95% or more homologous to the nucleotide sequence shown in the Figure sheets or a fragment of this sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under moderate to stringent conditions, to the nucleotide sequence shown in the Figure sheets or a fragment of the sequence. Allelic variants can readily be determined by genetic locus of the encoding gene. RH panel mapping shows the gene encoding the transporter proteins of the present invention is found on chromosome 17 near markers SHGC-56719 and SHGC-58932 (LOD=15.9 and 15.68).

Figure 3 provides information on SNPs that have been found in the gene encoding the transporter proteins of the present invention. The following variations were seen: g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a peptide at least 60-70% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 60%, at least about 70%, or at least about 80% or more

homologous to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65C. Examples of moderate to low stringency hybridization conditions are well known in the art.

Nucleic Acid Molecule Uses

The nucleic acid molecules of the present invention are useful for probes, primers, chemical intermediates, and in biological assays. The nucleic acid molecules are useful as a hybridization probe for messenger RNA, transcript/cDNA and genomic DNA to isolate full-length cDNA and genomic clones encoding the peptide described in Figure 2 and to isolate cDNA and genomic clones that correspond to variants (alleles, orthologs, etc.) producing the same or related peptides shown in Figure 2. As illustrated in Figure 3, identified SNP variations include g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t.

The probe can correspond to any sequence along the entire length of the nucleic acid molecules provided in the Figures. Accordingly, it could be derived from 5' noncoding regions, the coding region, and 3' noncoding regions. However, as discussed, fragments are not to be construed as encompassing fragments disclosed prior to the present invention.

The nucleic acid molecules are also useful as primers for PCR to amplify any given region of a nucleic acid molecule and are useful to synthesize antisense molecules of desired length and sequence.

The nucleic acid molecules are also useful for constructing recombinant vectors. Such vectors include expression vectors that express a portion of, or all of, the peptide sequences. Vectors also include insertion vectors, used to integrate into another nucleic acid molecule sequence, such as into the cellular genome, to alter *in situ* expression of a gene and/or gene product. For example, an endogenous coding sequence can be replaced via homologous recombination with all or part of the coding region containing one or more specifically introduced mutations.

The nucleic acid molecules are also useful for expressing antigenic portions of the proteins.

The nucleic acid molecules are also useful as probes for determining the chromosomal positions of the nucleic acid molecules by means of *in situ* hybridization methods. RH panel

mapping shows the gene encoding the transporter proteins of the present invention is found on chromosome 17 near markers SHGC-56719 and SHGC-58932 (LOD=15.9 and 15.68).

The nucleic acid molecules are also useful in making vectors containing the gene regulatory regions of the nucleic acid molecules of the present invention.

The nucleic acid molecules are also useful for designing ribozymes corresponding to all, or a part, of the mRNA produced from the nucleic acid molecules described herein.

The nucleic acid molecules are also useful for making vectors that express part, or all, of the peptides.

The nucleic acid molecules are also useful for constructing host cells expressing a part, or all, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful for constructing transgenic animals expressing all, or a part, of the nucleic acid molecules and peptides.

The nucleic acid molecules are also useful as hybridization probes for determining the presence, level, form and distribution of nucleic acid expression. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen.

Accordingly, the probes can be used to detect the presence of, or to determine levels of, a specific nucleic acid molecule in cells, tissues, and in organisms. The nucleic acid whose level is determined can be DNA or RNA. Accordingly, probes corresponding to the peptides described herein can be used to assess expression and/or gene copy number in a given cell, tissue, or organism. These uses are relevant for diagnosis of disorders involving an increase or decrease in transporter protein expression relative to normal results.

In vitro techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detecting DNA include Southern hybridizations and *in situ* hybridization.

Probes can be used as a part of a diagnostic test kit for identifying cells or tissues that express a transporter protein, such as by measuring a level of a transporter-encoding nucleic acid in a sample of cells from a subject e.g., mRNA or genomic DNA, or determining if a transporter gene

has been mutated. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen.

Nucleic acid expression assays are useful for drug screening to identify compounds that modulate transporter nucleic acid expression.

The invention thus provides a method for identifying a compound that can be used to treat a disorder associated with nucleic acid expression of the transporter gene, particularly biological and pathological processes that are mediated by the transporter in cells and tissues that express it. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas. The method typically includes assaying the ability of the compound to modulate the expression of the transporter nucleic acid and thus identifying a compound that can be used to treat a disorder characterized by undesired transporter nucleic acid expression. The assays can be performed in cell-based and cell-free systems. Cell-based assays include cells naturally expressing the transporter nucleic acid or recombinant cells genetically engineered to express specific nucleic acid sequences.

The assay for transporter nucleic acid expression can involve direct assay of nucleic acid levels, such as mRNA levels, or on collateral compounds involved in the signal pathway. Further, the expression of genes that are up- or down-regulated in response to the transporter protein signal pathway can also be assayed. In this embodiment the regulatory regions of these genes can be operably linked to a reporter gene such as luciferase.

Thus, modulators of transporter gene expression can be identified in a method wherein a cell is contacted with a candidate compound and the expression of mRNA determined. The level of expression of transporter mRNA in the presence of the candidate compound is compared to the level of expression of transporter mRNA in the absence of the candidate compound. The candidate

compound can then be identified as a modulator of nucleic acid expression based on this comparison and be used, for example to treat a disorder characterized by aberrant nucleic acid expression. When expression of mRNA is statistically significantly greater in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of nucleic acid expression. When nucleic acid expression is statistically significantly less in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of nucleic acid expression.

The invention further provides methods of treatment, with the nucleic acid as a target, using a compound identified through drug screening as a gene modulator to modulate transporter nucleic acid expression in cells and tissues that express the transporter. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen. Modulation includes both up-regulation (i.e. activation or agonization) or down-regulation (suppression or antagonization) or nucleic acid expression.

Alternatively, a modulator for transporter nucleic acid expression can be a small molecule or drug identified using the screening assays described herein as long as the drug or small molecule inhibits the transporter nucleic acid expression in the cells and tissues that express the protein. Independent lines of evidence show expression of splice form 1 in fetal tissues such as brain and kidney; differentiated tissues such as brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas; and neoplastic tissues such as germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendrogliomas, chronic lymphotic leukemic B-cells, glioblastomas, and well-differentiated endometrial adenocarcinomas.

The nucleic acid molecules are also useful for monitoring the effectiveness of modulating compounds on the expression or activity of the transporter gene in clinical trials or in a treatment regimen. Thus, the gene expression pattern can serve as a barometer for the continuing effectiveness of treatment with the compound, particularly with compounds to which a patient can develop resistance. The gene expression pattern can also serve as a marker indicative of a

physiological response of the affected cells to the compound. Accordingly, such monitoring would allow either increased administration of the compound or the administration of alternative compounds to which the patient has not become resistant. Similarly, if the level of nucleic acid expression falls below a desirable level, administration of the compound could be commensurately decreased.

The nucleic acid molecules are also useful in diagnostic assays for qualitative changes in transporter nucleic acid expression, and particularly in qualitative changes that lead to pathology. The nucleic acid molecules can be used to detect mutations in transporter genes and gene expression products such as mRNA. The nucleic acid molecules can be used as hybridization probes to detect naturally occurring genetic mutations in the transporter gene and thereby to determine whether a subject with the mutation is at risk for a disorder caused by the mutation. Mutations include deletion, addition, or substitution of one or more nucleotides in the gene, chromosomal rearrangement, such as inversion or transposition, modification of genomic DNA, such as aberrant methylation patterns or changes in gene copy number, such as amplification. Detection of a mutated form of the transporter gene associated with a dysfunction provides a diagnostic tool for an active disease or susceptibility to disease when the disease results from overexpression, underexpression, or altered expression of a transporter protein.

Individuals carrying mutations in the transporter gene can be detected at the nucleic acid level by a variety of techniques. Figure 3 provides information on SNPs that have been found in the gene encoding the transporter proteins of the present invention. The following variations were seen: g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t. RH panel mapping shows the gene encoding the transporter proteins of the present invention is found on chromosome 17 near markers SHGC-56719 and SHGC-58932 (LOD=15.9 and 15.68). Genomic DNA can be analyzed directly or can be amplified by using PCR prior to analysis. RNA or cDNA can be used in the same way. In some uses, detection of the mutation involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.*, *Science 241*:1077-1080 (1988); and Nakazawa *et al.*, *PNAS 91*:360-364 (1994)), the latter of which can be particularly useful for detecting point mutations in the gene (see Abravaya *et al.*, *Nucleic Acids Res. 23*:675-682 (1995)). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample,

contacting the nucleic acid sample with one or more primers which specifically hybridize to a gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. Deletions and insertions can be detected by a change in size of the amplified product compared to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to normal RNA or antisense DNA sequences.

Alternatively, mutations in a transporter gene can be directly identified, for example, by alterations in restriction enzyme digestion patterns determined by gel electrophoresis.

Further, sequence-specific ribozymes (U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site. Perfectly matched sequences can be distinguished from mismatched sequences by nuclease cleavage digestion assays or by differences in melting temperature.

Sequence changes at specific locations can also be assessed by nuclease protection assays such as RNase and S1 protection or the chemical cleavage method. Furthermore, sequence differences between a mutant transporter gene and a wild-type gene can be determined by direct DNA sequencing. A variety of automated sequencing procedures can be utilized when performing the diagnostic assays (Naeve, C.W., (1995) *Biotechniques 19*:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.*, *Adv. Chromatogr. 36*:127-162 (1996); and Griffin *et al.*, *Appl. Biochem. Biotechnol. 38*:147-159 (1993)).

Other methods for detecting mutations in the gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA duplexes (Myers *et al.*, *Science 230*:1242 (1985)); Cotton *et al.*, *PNAS 85*:4397 (1988); Saleeba *et al.*, *Meth. Enzymol. 217*:286-295 (1992)), electrophoretic mobility of mutant and wild type nucleic acid is compared (Orita *et al.*, *PNAS 86*:2766 (1989); Cotton *et al.*, *Mutat. Res. 285*:125-144 (1993); and Hayashi *et al.*, *Genet. Anal. Tech. Appl. 9*:73-79 (1992)), and movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (Myers *et al.*, *Nature 313*:495 (1985)). Examples of other techniques for detecting point mutations include selective oligonucleotide hybridization, selective amplification, and selective primer extension.

The nucleic acid molecules are also useful for testing an individual for a genotype that while not necessarily causing the disease, nevertheless affects the treatment modality. Thus, the nucleic acid molecules can be used to study the relationship between an individual's genotype and the

individual's response to a compound used for treatment (pharmacogenomic relationship). Accordingly, the nucleic acid molecules described herein can be used to assess the mutation content of the transporter gene in an individual in order to select an appropriate compound or dosage regimen for treatment. Figure 3 provides information on SNPs that have been found in the gene encoding the transporter proteins of the present invention. The following variations were seen: g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t.

Thus nucleic acid molecules displaying genetic variations that affect treatment provide a diagnostic target that can be used to tailor treatment in an individual. Accordingly, the production of recombinant cells and animals containing these polymorphisms allow effective clinical design of treatment compounds and dosage regimens.

The nucleic acid molecules are thus useful as antisense constructs to control transporter gene expression in cells, tissues, and organisms. A DNA antisense nucleic acid molecule is designed to be complementary to a region of the gene involved in transcription, preventing transcription and hence production of transporter protein. An antisense RNA or DNA nucleic acid molecule would hybridize to the mRNA and thus block translation of mRNA into transporter protein.

Alternatively, a class of antisense molecules can be used to inactivate mRNA in order to decrease expression of transporter nucleic acid. Accordingly, these molecules can treat a disorder characterized by abnormal or undesired transporter nucleic acid expression. This technique involves cleavage by means of ribozymes containing nucleotide sequences complementary to one or more regions in the mRNA that attenuate the ability of the mRNA to be translated. Possible regions include coding regions and particularly coding regions corresponding to the catalytic and other functional activities of the transporter protein, such as ligand binding.

The nucleic acid molecules also provide vectors for gene therapy in patients containing cells that are aberrant in transporter gene expression. Thus, recombinant cells, which include the patient's cells that have been engineered *ex vivo* and returned to the patient, are introduced into an individual where the cells produce the desired transporter protein to treat the individual.

The invention also encompasses kits for detecting the presence of a transporter nucleic acid in a biological sample. Screening of tissue specific cDNA libraries for cDNA retrieval showed expression of splice form 1 in fetal brain, brain, pituitary gland, heart, leukocytes, kidney, liver, thyroid, lung, placenta, skeletal muscle, fetal kidney, small intestine, prostate, testis, adrenal gland, bone marrow, and pancreas. Additionally, BLAST hits to ESTs derived from tissue

specific libraries shows expression of splice form 1 in germ cell tumors, lung carcinoid tissue, brain anaplastic oligodendroglioma, chronic lymphotic leukemia B-cells, infant brain (73 days post natal), placenta, gliobloastoma, well-differentiated endometrial adenocarcinoma, and fetal liver and spleen. For example, the kit can comprise reagents such as a labeled or labelable nucleic acid or agent capable of detecting transporter nucleic acid in a biological sample; means for determining the amount of transporter nucleic acid in the sample; and means for comparing the amount of transporter nucleic acid in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect transporter protein mRNA or DNA.

Nucleic Acid Arrays

The present invention further provides nucleic acid detection kits, such as arrays or microarrays of nucleic acid molecules that are based on the sequence information provided in Figures 1 and 3 (SEQ ID NOS:1, 3, and 4).

As used herein "Arrays" or "Microarrays" refers to an array of distinct polynucleotides or oligonucleotides synthesized on a substrate, such as paper, nylon or other type of membrane, filter, chip, glass slide, or any other suitable solid support. In one embodiment, the microarray is prepared and used according to the methods described in US Patent 5,837,832, Chee *et al.*, PCT application W095/11995 (Chee *et al.*), Lockhart, D. J. *et al.* (1996; Nat. Biotech. 14: 1675-1680) and Schena, M. *et al.* (1996; Proc. Natl. Acad. Sci. 93: 10614-10619), all of which are incorporated herein in their entirety by reference. In other embodiments, such arrays are produced by the methods described by Brown *et al.*, US Patent No. 5,807,522.

The microarray or detection kit is preferably composed of a large number of unique, single-stranded nucleic acid sequences, usually either synthetic antisense oligonucleotides or fragments of cDNAs, fixed to a solid support. The oligonucleotides are preferably about 6-60 nucleotides in length, more preferably 15-30 nucleotides in length, and most preferably about 20-25 nucleotides in length. For a certain type of microarray or detection kit, it may be preferable to use oligonucleotides that are only 7-20 nucleotides in length. The microarray or detection kit may contain oligonucleotides that cover the known 5', or 3', sequence, sequential oligonucleotides that cover the full length sequence; or unique oligonucleotides selected from particular areas along the length of the sequence. Polynucleotides used in the microarray or detection kit may be oligonucleotides that are specific to a gene or genes of interest.

In order to produce oligonucleotides to a known sequence for a microarray or detection kit, the gene(s) of interest (or an ORF identified from the contigs of the present invention) is typically examined using a computer algorithm which starts at the 5' or at the 3' end of the nucleotide sequence. Typical algorithms will then identify oligomers of defined length that are unique to the gene, have a GC content within a range suitable for hybridization, and lack predicted secondary structure that may interfere with hybridization. In certain situations it may be appropriate to use pairs of oligonucleotides on a microarray or detection kit. The "pairs" will be identical, except for one nucleotide that preferably is located in the center of the sequence. The second oligonucleotide in the pair (mismatched by one) serves as a control. The number of oligonucleotide pairs may range from two to one million. The oligomers are synthesized at designated areas on a substrate using a light-directed chemical process. The substrate may be paper, nylon or other type of membrane, filter, chip, glass slide or any other suitable solid support.

In another aspect, an oligonucleotide may be synthesized on the surface of the substrate by using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application W095/251116 (Baldeschweiler *et al.*) which is incorporated herein in its entirety by reference. In another aspect, a "gridded" array analogous to a dot (or slot) blot may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedures. An array, such as those described above, may be produced by hand or by using available devices (slot blot or dot blot apparatus), materials (any suitable solid support), and machines (including robotic instruments), and may contain 8, 24, 96, 384, 1536, 6144 or more oligonucleotides, or any other number between two and one million which lends itself to the efficient use of commercially available instrumentation.

In order to conduct sample analysis using a microarray or detection kit, the RNA or DNA from a biological sample is made into hybridization probes. The mRNA is isolated, and cDNA is produced and used as a template to make antisense RNA (aRNA). The aRNA is amplified in the presence of fluorescent nucleotides, and labeled probes are incubated with the microarray or detection kit so that the probe sequences hybridize to complementary oligonucleotides of the microarray or detection kit. Incubation conditions are adjusted so that hybridization occurs with precise complementary matches or with various degrees of less complementarity. After removal of nonhybridized probes, a scanner is used to determine the levels and patterns of fluorescence. The scanned images are examined to determine degree of complementarity and the relative

abundance of each oligonucleotide sequence on the microarray or detection kit. The biological samples may be obtained from any bodily fluids (such as blood, urine, saliva, phlegm, gastric juices, etc.), cultured cells, biopsies, or other tissue preparations. A detection system may be used to measure the absence, presence, and amount of hybridization for all of the distinct sequences simultaneously. This data may be used for large-scale correlation studies on the sequences, expression patterns, mutations, variants, or polymorphisms among samples.

Using such arrays, the present invention provides methods to identify the expression of the transporter proteins/peptides of the present invention. In detail, such methods comprise incubating a test sample with one or more nucleic acid molecules and assaying for binding of the nucleic acid molecule with components within the test sample. Such assays will typically involve arrays comprising many genes, at least one of which is a gene of the present invention and or alleles of the transporter gene of the present invention. Figure 3 provides information on SNPs that have been found in the gene encoding the transporter proteins of the present invention. The following variations were seen: g30344a, a31170g, c16256t, a13376t, t12210c, g12072c, g11922t, -11903a, c10009g, c4519t, a4181g, a20952c, t20987c, g21620a, t21795c, a22753t, g22945a, g23032a, g23738a, t23952g, a24123g, c24527-, c24691t, g25015a, and g25191t.

Conditions for incubating a nucleic acid molecule with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid molecule used in the assay. One skilled in the art will recognize that any one of the commonly available hybridization, amplification or array assay formats can readily be adapted to employ the novel fragments of the Human genome disclosed herein. Examples of such assays can be found in Chard, T, *An Introduction to Radioimmunoassay and Related Techniques,* Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G. R. *et al., Techniques in Immunocytochemistry,* Academic Press, Orlando, FL Vol. 1 (1 982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., *Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology,* Elsevier Science Publishers, Amsterdam, The Netherlands (1985).

The test samples of the present invention include cells, protein or membrane extracts of cells. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing nucleic acid extracts or of cells are well known in the art and can be readily be adapted in order to obtain a sample that is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention.

Specifically, the invention provides a compartmentalized kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the nucleic acid molecules that can bind to a fragment of the Human genome disclosed herein; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound nucleic acid.

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers, strips of plastic, glass or paper, or arraying material such as silica. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the nucleic acid probe, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound probe. One skilled in the art will readily recognize that the previously unidentified transporter gene of the present invention can be routinely identified using the sequence information disclosed herein can be readily incorporated into one of the established kit formats which are well known in the art, particularly expression arrays.

Vectors/host cells

The invention also provides vectors containing the nucleic acid molecules described herein. The term "vector" refers to a vehicle, preferably a nucleic acid molecule, which can transport the nucleic acid molecules. When the vector is a nucleic acid molecule, the nucleic acid molecules are covalently linked to the vector nucleic acid. With this aspect of the invention, the vector includes a plasmid, single or double stranded phage, a single or double stranded RNA or DNA viral vector, or artificial chromosome, such as a BAC, PAC, YAC, OR MAC.

A vector can be maintained in the host cell as an extrachromosomal element where it replicates and produces additional copies of the nucleic acid molecules. Alternatively, the vector may integrate into the host cell genome and produce additional copies of the nucleic acid molecules when the host cell replicates.

The invention provides vectors for the maintenance (cloning vectors) or vectors for expression (expression vectors) of the nucleic acid molecules. The vectors can function in procaryotic or eukaryotic cells or in both (shuttle vectors).

Expression vectors contain cis-acting regulatory regions that are operably linked in the vector to the nucleic acid molecules such that transcription of the nucleic acid molecules is allowed in a host cell. The nucleic acid molecules can be introduced into the host cell with a separate nucleic acid molecule capable of affecting transcription. Thus, the second nucleic acid molecule may provide a trans-acting factor interacting with the cis-regulatory control region to allow transcription of the nucleic acid molecules from the vector. Alternatively, a trans-acting factor may be supplied by the host cell. Finally, a trans-acting factor can be produced from the vector itself. It is understood, however, that in some embodiments, transcription and/or translation of the nucleic acid molecules can occur in a cell-free system.

The regulatory sequence to which the nucleic acid molecules described herein can be operably linked include promoters for directing mRNA transcription. These include, but are not limited to, the left promoter from bacteriophage λ, the lac, TRP, and TAC promoters from *E. coli*, the early and late promoters from SV40, the CMV immediate early promoter, the adenovirus early and late promoters, and retrovirus long-terminal repeats.

In addition to control regions that promote transcription, expression vectors may also include regions that modulate transcription, such as repressor binding sites and enhancers. Examples include the SV40 enhancer, the cytomegalovirus immediate early enhancer, polyoma enhancer, adenovirus enhancers, and retrovirus LTR enhancers.

In addition to containing sites for transcription initiation and control, expression vectors can also contain sequences necessary for transcription termination and, in the transcribed region a ribosome binding site for translation. Other regulatory control elements for expression include initiation and termination codons as well as polyadenylation signals. The person of ordinary skill in the art would be aware of the numerous regulatory sequences that are useful in expression vectors. Such regulatory sequences are described, for example, in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

A variety of expression vectors can be used to express a nucleic acid molecule. Such vectors include chromosomal, episomal, and virus-derived vectors, for example vectors derived from bacterial plasmids, from bacteriophage, from yeast episomes, from yeast chromosomal elements, including yeast artificial chromosomes, from viruses such as baculoviruses,

papovaviruses such as SV40, Vaccinia viruses, adenoviruses, poxviruses, pseudorabies viruses, and retroviruses. Vectors may also be derived from combinations of these sources such as those derived from plasmid and bacteriophage genetic elements, e.g. cosmids and phagemids. Appropriate cloning and expression vectors for prokaryotic and eukaryotic hosts are described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual. 2nd. ed.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989).

The regulatory sequence may provide constitutive expression in one or more host cells (i.e. tissue specific) or may provide for inducible expression in one or more cell types such as by temperature, nutrient additive, or exogenous factor such as a hormone or other ligand. A variety of vectors providing for constitutive and inducible expression in prokaryotic and eukaryotic hosts are well known to those of ordinary skill in the art.

The nucleic acid molecules can be inserted into the vector nucleic acid by well-known methodology. Generally, the DNA sequence that will ultimately be expressed is joined to an expression vector by cleaving the DNA sequence and the expression vector with one or more restriction enzymes and then ligating the fragments together. Procedures for restriction enzyme digestion and ligation are well known to those of ordinary skill in the art.

The vector containing the appropriate nucleic acid molecule can be introduced into an appropriate host cell for propagation or expression using well-known techniques. Bacterial cells include, but are not limited to, *E. coli*, *Streptomyces*, and *Salmonella typhimurium*. Eukaryotic cells include, but are not limited to, yeast, insect cells such as *Drosophila*, animal cells such as COS and CHO cells, and plant cells.

As described herein, it may be desirable to express the peptide as a fusion protein. Accordingly, the invention provides fusion vectors that allow for the production of the peptides. Fusion vectors can increase the expression of a recombinant protein, increase the solubility of the recombinant protein, and aid in the purification of the protein by acting for example as a ligand for affinity purification. A proteolytic cleavage site may be introduced at the junction of the fusion moiety so that the desired peptide can ultimately be separated from the fusion moiety. Proteolytic enzymes include, but are not limited to, factor Xa, thrombin, and enterotransporter. Typical fusion expression vectors include pGEX (Smith *et al.*, *Gene 67*:31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein. Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann

et al., *Gene 69*:301-315 (1988)) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology 185*:60-89 (1990)).

Recombinant protein expression can be maximized in host bacteria by providing a genetic background wherein the host cell has an impaired capacity to proteolytically cleave the recombinant protein. (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Alternatively, the sequence of the nucleic acid molecule of interest can be altered to provide preferential codon usage for a specific host cell, for example *E. coli*. (Wada *et al.*, *Nucleic Acids Res. 20*:2111-2118 (1992)).

The nucleic acid molecules can also be expressed by expression vectors that are operative in yeast. Examples of vectors for expression in yeast e.g., *S. cerevisiae* include pYepSec1 (Baldari, *et al.*, *EMBO J. 6*:229-234 (1987)), pMFa (Kurjan *et al.*, *Cell 30*:933-943(1982)), pJRY88 (Schultz *et al.*, *Gene 54*:113-123 (1987)), and pYES2 (Invitrogen Corporation, San Diego, CA).

The nucleic acid molecules can also be expressed in insect cells using, for example, baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith *et al.*, *Mol. Cell Biol. 3*:2156-2165 (1983)) and the pVL series (Lucklow *et al.*, *Virology 170*:31-39 (1989)).

In certain embodiments of the invention, the nucleic acid molecules described herein are expressed in mammalian cells using mammalian expression vectors. Examples of mammalian expression vectors include pCDM8 (Seed, B. *Nature 329*:840(1987)) and pMT2PC (Kaufman *et al.*, *EMBO J. 6*:187-195 (1987)).

The expression vectors listed herein are provided by way of example only of the well-known vectors available to those of ordinary skill in the art that would be useful to express the nucleic acid molecules. The person of ordinary skill in the art would be aware of other vectors suitable for maintenance propagation or expression of the nucleic acid molecules described herein. These are found for example in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

The invention also encompasses vectors in which the nucleic acid sequences described herein are cloned into the vector in reverse orientation, but operably linked to a regulatory sequence that permits transcription of antisense RNA. Thus, an antisense transcript can be produced to all, or to a portion, of the nucleic acid molecule sequences described herein, including both coding and non-coding regions. Expression of this antisense RNA is subject to each of the parameters

described above in relation to expression of the sense RNA (regulatory sequences, constitutive or inducible expression, tissue-specific expression).

The invention also relates to recombinant host cells containing the vectors described herein. Host cells therefore include prokaryotic cells, lower eukaryotic cells such as yeast, other eukaryotic cells such as insect cells, and higher eukaryotic cells such as mammalian cells.

The recombinant host cells are prepared by introducing the vector constructs described herein into the cells by techniques readily available to the person of ordinary skill in the art. These include, but are not limited to, calcium phosphate transfection, DEAE-dextran-mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, lipofection, and other techniques such as those found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Host cells can contain more than one vector. Thus, different nucleotide sequences can be introduced on different vectors of the same cell. Similarly, the nucleic acid molecules can be introduced either alone or with other nucleic acid molecules that are not related to the nucleic acid molecules such as those providing trans-acting factors for expression vectors. When more than one vector is introduced into a cell, the vectors can be introduced independently, co-introduced or joined to the nucleic acid molecule vector.

In the case of bacteriophage and viral vectors, these can be introduced into cells as packaged or encapsulated virus by standard procedures for infection and transduction. Viral vectors can be replication-competent or replication-defective. In the case in which viral replication is defective, replication will occur in host cells providing functions that complement the defects.

Vectors generally include selectable markers that enable the selection of the subpopulation of cells that contain the recombinant vector constructs. The marker can be contained in the same vector that contains the nucleic acid molecules described herein or may be on a separate vector. Markers include tetracycline or ampicillin-resistance genes for prokaryotic host cells and dihydrofolate reductase or neomycin resistance for eukaryotic host cells. However, any marker that provides selection for a phenotypic trait will be effective.

While the mature proteins can be produced in bacteria, yeast, mammalian cells, and other cells under the control of the appropriate regulatory sequences, cell- free transcription and translation systems can also be used to produce these proteins using RNA derived from the DNA constructs described herein.

Where secretion of the peptide is desired, which is difficult to achieve with multi-transmembrane domain containing proteins such as transporters, appropriate secretion signals are incorporated into the vector. The signal sequence can be endogenous to the peptides or heterologous to these peptides.

Where the peptide is not secreted into the medium, which is typically the case with transporters, the protein can be isolated from the host cell by standard disruption procedures, including freeze thaw, sonication, mechanical disruption, use of lysing agents and the like. The peptide can then be recovered and purified by well-known purification methods including ammonium sulfate precipitation, acid extraction, anion or cationic exchange chromatography, phosphocellulose chromatography, hydrophobic-interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography, or high performance liquid chromatography.

It is also understood that depending upon the host cell in recombinant production of the peptides described herein, the peptides can have various glycosylation patterns, depending upon the cell, or maybe non-glycosylated as when produced in bacteria. In addition, the peptides may include an initial modified methionine in some cases as a result of a host-mediated process.

Uses of vectors and host cells

The recombinant host cells expressing the peptides described herein have a variety of uses. First, the cells are useful for producing a transporter protein or peptide that can be further purified to produce desired amounts of transporter protein or fragments. Thus, host cells containing expression vectors are useful for peptide production.

Host cells are also useful for conducting cell-based assays involving the transporter protein or transporter protein fragments, such as those described above as well as other formats known in the art. Thus, a recombinant host cell expressing a native transporter protein is useful for assaying compounds that stimulate or inhibit transporter protein function.

Host cells are also useful for identifying transporter protein mutants in which these functions are affected. If the mutants naturally occur and give rise to a pathology, host cells containing the mutations are useful to assay compounds that have a desired effect on the mutant transporter protein (for example, stimulating or inhibiting function) which may not be indicated by their effect on the native transporter protein.

Genetically engineered host cells can be further used to produce non-human transgenic animals. A transgenic animal is preferably a mammal, for example a rodent, such as a rat or mouse,

in which one or more of the cells of the animal include a transgene. A transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal in one or more cell types or tissues of the transgenic animal. These animals are useful for studying the function of a transporter protein and identifying and evaluating modulators of transporter protein activity. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians.

A transgenic animal can be produced by introducing nucleic acid into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Any of the transporter protein nucleotide sequences can be introduced as a transgene into the genome of a non-human animal, such as a mouse.

Any of the regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. This includes intronic sequences and polyadenylation signals, if not already included. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the transporter protein to particular cells.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of transgenic mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene can further be bred to other transgenic animals carrying other transgenes. A transgenic animal also includes animals in which the entire animal or tissues in the animal have been produced using the homologously recombinant host cells described herein.

In another embodiment, transgenic non-human animals can be produced which contain selected systems that allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al. PNAS 89*:6232-6236 (1992). Another example of a recombinase system is the FLP recombinase system of *S. cerevisiae* (O'Gorman *et al. Science 251*:1351-1355 (1991). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein

is required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al. Nature 385*:810-813 (1997) and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G_0 phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring born of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

Transgenic animals containing recombinant cells that express the peptides described herein are useful to conduct the assays described herein in an *in vivo* context. Accordingly, the various physiological factors that are present *in vivo* and that could effect ligand binding, transporter protein activation, and signal transduction, may not be evident from *in vitro* cell-free or cell-based assays. Accordingly, it is useful to provide non-human transgenic animals to assay *in vivo* transporter protein function, including ligand interaction, the effect of specific mutant transporter proteins on transporter protein function and ligand interaction, and the effect of chimeric transporter proteins. It is also possible to assess the effect of null mutations, that is mutations that substantially or completely eliminate one or more transporter protein functions.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of molecular biology or related fields are intended to be within the scope of the following claims.

Claims

That which is claimed is:

1. An isolated peptide consisting of an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5;

(b) an amino acid sequence of an allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(c) an amino acid sequence of an ortholog of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4; and

(d) a fragment of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said fragment comprises at least 10 contiguous amino acids.

2. An isolated peptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5;

(b) an amino acid sequence of an allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said allelic variant is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(c) an amino acid sequence of an ortholog of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said ortholog is encoded by a nucleic acid molecule that hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4; and

(d) a fragment of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said fragment comprises at least 10 contiguous amino acids.

3. An isolated antibody that selectively binds to a peptide of claim 2.

4. An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5;

(b) a nucleotide sequence that encodes of an allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

5. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5;

(b) a nucleotide sequence that encodes an allelic variant of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(c) a nucleotide sequence that encodes an ortholog of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said nucleotide sequence hybridizes under stringent conditions to the opposite strand of a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4;

(d) a nucleotide sequence that encodes a fragment of an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5, wherein said fragment comprises at least 10 contiguous amino acids; and

(e) a nucleotide sequence that is the complement of a nucleotide sequence of (a)-(d).

6. A gene chip comprising a nucleic acid molecule of claim 5.

7. A transgenic non-human animal comprising a nucleic acid molecule of claim 5.

8. A nucleic acid vector comprising a nucleic acid molecule of claim 5.

9. A host cell containing the vector of claim 8.

10. A method for producing any of the peptides of claim 1 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

11. A method for producing any of the peptides of claim 2 comprising introducing a nucleotide sequence encoding any of the amino acid sequences in (a)-(d) into a host cell, and culturing the host cell under conditions in which the peptides are expressed from the nucleotide sequence.

12. A method for detecting the presence of any of the peptides of claim 2 in a sample, said method comprising contacting said sample with a detection agent that specifically allows detection of the presence of the peptide in the sample and then detecting the presence of the peptide.

13. A method for detecting the presence of a nucleic acid molecule of claim 5 in a sample, said method comprising contacting the sample with an oligonucleotide that hybridizes to said nucleic acid molecule under stringent conditions and determining whether the oligonucleotide binds to said nucleic acid molecule in the sample.

14. A method for identifying a modulator of a peptide of claim 2, said method comprising contacting said peptide with an agent and determining if said agent has modulated the function or activity of said peptide.

15. The method of claim 14, wherein said agent is administered to a host cell comprising an expression vector that expresses said peptide.

16. A method for identifying an agent that binds to any of the peptides of claim 2, said method comprising contacting the peptide with an agent and assaying the contacted mixture to determine whether a complex is formed with the agent bound to the peptide.

17. A pharmaceutical composition comprising an agent identified by the method of claim 16 and a pharmaceutically acceptable carrier therefor.

18. A method for treating a disease or condition mediated by a human transporter protein, said method comprising administering to a patient a pharmaceutically effective amount of an agent identified by the method of claim 16.

19. A method for identifying a modulator of the expression of a peptide of claim 2, said method comprising contacting a cell expressing said peptide with an agent, and determining if said agent has modulated the expression of said peptide.

20. An isolated human transporter peptide having an amino acid sequence that shares at least 70% homology with an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5.

21. A peptide according to claim 20 that shares at least 90 percent homology with an amino acid sequence selected from the group consisting of SEQ ID NOS:2 and 5.

22. An isolated nucleic acid molecule encoding a human transporter peptide, said nucleic acid molecule sharing at least 80 percent homology with a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4.

23. A nucleic acid molecule according to claim 22 that shares at least 90 percent homology with a nucleic acid molecule selected from the group consisting of SEQ ID NOS:1, 3, and 4.

SPLICE FORM 1:

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      1  AACAGCACGA GGGCGGACCC AGCTGTGGCG ACGCCAGGAG ACCCCAAGCT
     51  GCATCGCCGA GTGGAAGCAA CTAGAACTCC AGGGCTGTGA AAGCCACAGG
    101  TGGGGGCTGA GCGAGGCGTG GCCTCAGGAG CGGAGGACCC CCCCACTCTC
    151  CCTCGAGCGC CGCAGTCCAC CGTAGCGGGT GGAGCCCGCC TTGGTGCGCA
    201  GTTGGAAAAC CTCGGAGCCC CGCTGGATCT CCTGGCTGCC ACCCGCACCC
    251  CCCGCCAGCC TACGCCCCAC CGTAGAGATG CCTTCTTCGG TGACGGCGCT
    301  GGGTCAGGCC AGGTCCTCTG GCCCCGGGAT GGCCCCGAGC GCCTGCTGCT
    351  GCTCCCCTGC GGCCCTGCAG AGGAGGCTGC CCATCCTGGC GTGGCTGCCC
    401  AGCTACTCCC TGCAGTGGCT GAAGATGGAT TTCGTCGCCG GCCTCTCAGT
    451  TGGCCTCACT GCCATTCCCC AGGCGCTGGC CTATGCTGAA GTGGCTGGAC
    501  TCCCGCCCCA GTATGGCCTC TACTCTGCCT TCATGGGCTG CTTCGTGTAT
    551  TTCTTCCTGG GCACCTCCCG GGATGTGACT CTGGGCCCCA CCGCCATTAT
    601  GTCCCTCCTG GTCTCCTTCT ACACCTTCCA TGAGCCCGCC TACGCTGTGC
    651  TGCTGGCCTT CCTGTCCGGC TGCATCCAGC TGGCCATGGG GGTCCTGCGT
    701  TTGGGGTTCC TGCTGGACTT CATTTCCTAC CCCGTCATTA AAGGCTTCAC
    751  CTCTGCTGCT GCCGTCACCA TCGGCTTTGG ACAGATCAAG AACCTGCTGG
    801  GACTACAGAA CATCCCCAGG CCGTTCTTCC TGCAGGTGTA CCACACCTTC
    851  CTCAGGATTG CAGAGACCAG GGTAGGTGAC GCCGTCCTGG GGCTGGTCTG
    901  CATGCTGCTG CTGCTGGTGC TGAAGCTGAT GCGGGACCAC GTGCCTCCCG
    951  TCCACCCCGA GATGCCCCCT GGTGTGCGGC TCAGCCGTGG GCTGGTCTGG
   1001  GCTGCCACGA CAGCTCGCAA CGCCCTGGTG GTCTCCTTCG CAGCCCTGGT
   1051  TGCGTACTCC TTCGAGGTGA CTGGATACCA GCCTTTCATC CTAACAGGGG
   1101  AGACAGCTGA GGGGCTCCCT CCAGTCCGGA TCCCGCCCTT CTCAGTGACC
   1151  ACAGCCAACG GGACGATCTC CTTCACCGAG ATGGTGCAGG ACATGGGAGC
   1201  CGGGCTGGCC GTGGTGCCCC TGATGGGCCT CCTGGAGAGC ATTGCGGTGG
   1251  CCAAAGCCTT CGCATCTCAG AATAATTACC GCATCGATGC CAACCAGGAG
   1301  CTGCTGGCCA TCGGTCTCAC CAACATGTTG GGCTCCCTCG TCTCCTCCTA
   1351  CCCGGTCACA GGCAGCTTTG GACGGACAGC CGTGAACGCT CAGTCGGGGG
   1401  TGTGCACCCC GGCGGGGGGC CTGGTGACGG GAGTGCTGGT GCTGCTGTCT
   1451  CTGGACTACC TGACCTCACT GTTCTACTAC ATCCCCAAGT CTGCCCTGGC
   1501  TGCCGTCATC ATCATGGCCG TGGCCCCGCT GTTCGACACC AAGATCTTCA
   1551  GGACGCTCTG GCGTGTTAAG AGGCTGGACC TGCTGCCCCT GTGCGTGACC
   1601  TTCCTGCTGT GCTTCTGGGA GGTGCAGTAC GGCATCCTGG CCGGGGCCCT
   1651  GGTGTCTCTG CTCATGCTCC TGCACTCTGC AGCCAGGCCT GAGACCAAGG
   1701  TGTCAGAGGG GCCGGTTCTG GTCCTGCAGC CGGCCAGCGG CCTGTCCTTC
   1751  CCTGCCATGG AGGCTCTGCG GGAGGAGATC CTAAGCCGGG CCCTGGAAGT
   1801  GTCCCCGCCA CGCTGCCTGG TCCTGGAGTG CACCCATGTC TGCAGCATCG
   1851  ACTACACTGT GGTGCTGGGA CTCGGCGAGC TCCTCCAGGA CTTCCAGAAG
   1901  CAGGGCGTCG CCCTGGCCTT TGTGGGCCTG CAGGTCCCCG TTCTCCGTGT
   1951  CCTGCTGTCC GCTGACCTGA AGGGGTTCCA GTACTTCTCT ACCCTGGAAG
   2001  AAGCAGAGAA GCACCTGAGG CAGGAGCCAG GGACCCAGCC CTACAACATC
   2051  AGAGAAGACT CCATTCTGGA CCAAAAGGTT GCCCTGCTCA AGGCATAATG
   2101  GGGCCACCCG TGGGCATCCA CAGTTTGCAG GGTGTTCCGG AAGGTTCTTG
   2151  TCACTGTGAT TGGATGCTGG ATGCCGCCTG ATAGACATGC TGGCCTGGCT
   2201  GAGAAACCCC TGAGCAGGTA ACCCAGGGAA GAGAAGGAAG CCAGGCCTGG
   2251  AGGTCCACGG CAGTGGGAGT GGGGCTCACT GGCTTCCTGT GGGATGACTG
   2301  GAAAATGACC TCGCTGCTGT TCCCTGGCAT GACCCTCTTT GGAAGAGTGG
   2351  TTTGGAGAGA GCCTTCTAGA ATGACAGACT GTGCGAGGAA GCAGGGGCAG
   2401  GGGTTTCCAG CCCGGGCTGT GCGAGGCATC CTGGGGCTGG CAGCACCTTC
   2451  CCGGCTCACC AGTGCCACCT GCGGGGGAGG GACGGGGCAG GCAGGAGTCT
   2501  GGGAGGCGGG TCCGCTCCTC TTGTCTGCGG CATCTGTGCT CTCCGAGAGA
   2551  AAACCAAGGT GTGTCAAATG ACGTCAAGTC TCTATTTAAA AATAATTTTG
   2601  TGTTTTCTAA ATGGAAAAAG TGATAGCTTT GGTGATTTTG TAAAAGTCAT
   2651  AAATGCTTAT TGTAAAAAAT ACAGGAAACC ACCCCTCACC CTGTCCACTT
   2701  GGGTGATCAT TCCAGACCCC TCCCCAAACA TGCATATGTA CCTGTCCGTC
   2751  AGTGTGTGGA TGTATGTTTA CAGTTCTACA TAAATGGGAT CATTTTATAC
   2801  ATGGTGCTCT GGAACCCACA TTTTTCATGC AGTCATTTGC AGTGAATTAT
   2851  TTATTGTGAT AATAAATAGC ATTAGAATAC AAGAAAAAAA AAAAAAAAAA
   2901  AAAAAAAAAA AAAAAAAAA (SEQ ID NO:1)
```

FEATURES:

5'UTR: 1-277
Start: 278
Stop: 2096
3'UTR: 2096-2919

SPLICE FORM 2:

```
       1  GCTGTGGCGA CGCCAGGAGA CCCCAAGCTG CATCGCCGAG TGGAAGCAAC
      51  TAGAACTCCA GGGCTGTGAA AGCCACAGGT GGGGGCTGAG CGAGGCGTGG
     101  CCTCAGGAGC GGAGGACCCC CCCACTCTCC CTCGAGCGCC GCAGTCCACC
     151  GTAGCGGGTG GAGCCCGCCT TGGTGCGCAG TTGGAAAACC TCGGAGCCCC
     201  GCTGGATCTC CTGGCTGCCA CCCGCACCCC CCGCCAGCCT ACGCCCCACC
     251  GTAGAGATGC CTTCTTCGGT GACGGCGCTG GGTCAGGCCA GGTCCTCTGG
     301  CCCCGGGATG GCCCCGAGCG CCTGCTGCTG CTCCCCTGCG GCCCTGCAGA
     351  GGAGGCTGCC CATCCTGGCG TGGCTGCCCA GCTACTCCCT GCAGTGGCTG
     401  AAGATGGATT TCGTCGCCGG CCTCTCAGTT GGCCTCACTG CCATTCCCCA
     451  GGCGCTGGCC TATGCTGAAG TGGCTGGACT CCCGCCCCAG TATGGCCTCT
     501  ACTCTGCCTT CATGGGCTGC TTCGTGTATT TCTTCCTGGG CACCTCCCGG
     551  GATGTGACTC TGGGCCCCAC CGCCATTATG TCCCTCCTGG TCTCCTTCTA
     601  CACCTTCCAT GAGCCCGCCT ACGCTGTGCT GCTGGCCTTC CTGTCCGGCT
     651  GCATCCAGCT GGCCATGGGG GTCCTGCGTT TGGCTCACAT CTCCCCTCAT
     701  CCTCTGGGAC TGGGTGGAGC CGGGACCAGC TCGATGTCCC CTCTTGGCTG
     751  GCCAGGGTTC CTGCTGGACT TCATTTCCTA CCCCGTCATT AAAGGCTTCA
     801  CCTCTGCTGC TGCCGTCACC ATCGGCTTTG GACAGATCAA GAACCTGCTG
     851  GGACTACAGA ACATCCCCAG GCCGTTCTTC CTGCAGGTGT ACCACACCTT
     901  CCTCAGGATT GCAGAGACCA GGGTAGGTGA CGCCGTCCTG GGGCTGGTCT
     951  GCATGCTGCT GCTGCTGGTG CTGAAGCTGA TGCGGGACCA CGTGCCTCCC
    1001  GTCCACCCCG AGATGCCCCC TGGTGTGCGG CTCAGCCGTG GGCTGGTCTG
    1051  GGCTGCCACG ACAGCTCGCA ACGCCCTGGT GGTCTCCTTC GCAGCCCTGG
    1101  TTGCGTACTC CTTCGAGGTG ACTGGATACC AGCCTTTCAT CCTAACAGGG
    1151  GAGACAGCTG AGGGGCTCCC TCCAGTCCGG ATCCCGCCCT TCTCAGTGAC
    1201  CACAGCCAAC GGGACGATCT CCTTCACCGA GATGGTGCAG GACATGGGAG
    1251  CCGGGCTGGC CGTGGTGCCC CTGATGGGCC TCCTGGAGAG CATTGCGGTG
    1301  GCCAAAGCCT TCGCATCTCA GAATAATTAC CGCATCGATG CCAACCAGGA
    1351  GCTGCTGGCC ATCGGTCTCA CCAACATGTT GGGCTCCCTC GTCTCCTCCT
    1401  ACCCGGTCAC AGGCAGCTTT GGACGGACAG CCGTGAACGC TCAGTCGGGG
    1451  GTGTGCACCC CGGCGGGGGG CCTGGTGACG GGAGTGCTGG TGCTGCTGTC
    1501  TCTGGACTAC CTGACCTCAC TGTTCTACTA CATCCCCAAG TCTGCCCTGG
    1551  CTGCCGTCAT CATCATGGCC GTGGCCCCGC TGTTCGACAC CAAGATCTTC
    1601  AGGACGCTCT GGCGTGTTAA GAGGCTGGAC CTGCTGCCCC TGTGGGTGAC
    1651  CTTCCTGCTG TGCTTCTGGG AGGTGCAGTA CGGCATCCTG GCCGGGGCCC
    1701  TGGTGTCTCT GCTCATGCTC CTGCACTCTG CAGCCAGGCC TGAGACCAAG
    1751  GTGTCAGAGG GGCCGGTTCT GGTCCTGCAG CCGGCCAGCG GCCTGTCCTT
    1801  CCCTGCCATG GAGGCTCTGC GGGAGGAGAT CCTAAGCCGG GCCCTGGAAG
    1851  TGTCCCCGCC ACGCTGCCTG GTCCTGGAGT GCACCCATGT CTGCAGCATC
    1901  GACTACACTG TGGTGCTGGG ACTCGGCGAG CTCCTCCAGG ACTTCCAGAA
    1951  GCAGGGCGTC GCCCTGGCCT TTGTGGGCCT GCAGGTCCCC GTTCTCCGTG
    2001  TCCTGCTGTC CGCTGACCTG AAGGGGTTCC AGTACTTCTC TACCCTGGAA
    2051  GAAGCAGAGA AGCACCTGAG GCAGGAGCCA GGGACCCAGC CCTACAACAT
    2101  CAGAGAAGAC TCCATTCTGG ACCAAAAGGT TGCCCTGCTC AAGGCATAAT
    2151  GGGGCCACCC GTGGGCATCC ACAGTTTGCA GGGTGTTCCG GAAGGTTCTT
    2201  GTCACTGTGA TTGGATGCTG GATGCCGCCT GATAGACATG CTGGCCTGGC
    2251  TGAGAAACCC CTGAGCAGGT AACCCAGGGA AGAGAAGGAA GCCAGGCCTG
    2301  GAGGTCCACG GCAGTGGGAG TGGGGCTCAC TGGCTTCCTG TGGGATGACT
    2351  GGAAAATGAC CTCGCTGCTG TTCCCTGGCA TGACCCTCTT TGGAAGAGTG
    2401  GTTTGGAGAG AGCCTTCTAG AATGACAGAC TGTGCGAGGA AGCAGGGGCA
    2451  GGGGTTTCCA GCCCGGGCTG TGCGAGGCAT CCTGGGGCTG GCAGCACCTT
    2501  CCCGGCTCAC CAGTGCCACC TGCGGGGGAG GGACGGGGCA GGCAGGAGTC
    2551  TGGGAGGCGG GTCCGCTCCT CTTGTCTGCG GCATCTGTGC TCTCCGAGAG
    2601  AAAACCAAGG TGTGTCAAAT GACGTCAAGT CTCTATTTAA AAATAATTTT
    2651  GTGTTTTCTA AATGGAAAAA GTGATAGCTT TGGTGATTTT GTAAAAGTCA
    2701  TAAATGCTTA TTGTAAAAAA TACAGGAAAC CACCCCTCAC CCTGTCCACT
    2751  TGGGTGATCA TTCCAGACCC CTCCCCAAAC ATGCATATGT ACCTGTCCGT
    2801  CAGTGTGTGG ATGTATGTTT ACAGTTCTAC ATAAATGGGA TCATTTTATA
    2851  CATGGTGCTC TGGAACCCAC ATTTTTCATG CAGTCATTTG CAGTGAATTA
    2901  TTTATTGTGA TAATAAATAG CATTAGAATA CAAAAAAAAA AAAAAAAAAA
    2951  AAAAA (SEQ ID NO:2)
```

FEATURES:
5' UTR: 1-257
Start: 257

Stop: 2147
3' UTR: 2150-2955

HOMOLOGOUS PROTEINS:
Top BLAST Hits:

	Score	E
SPLICE FORM 1:		
gi|7302719|gb|AAF57797.1| (AE003802) CG5002 gene product [Droso...	418	e-116
gi|7301881|gb|AAF56989.1| (AE003772) CG7912 gene product [Droso...	408	e-113
gi|5834394|gb|AAD53951.1| (AF180728) sulfate transporter [Droso...	388	e-107
gi|7301216|gb|AAF56347.1| (AE003749) Esp gene product [Drosophi...	387	e-106
gi|7301962|gb|AAF57068.1| (AE003774) CG9702 gene product [Droso...	351	8e-96
gi|7294633|gb|AAF49971.1| (AE003543) CG6928 gene product [Droso...	347	2e-94
gi|7300023|gb|AAF55195.1| (AE003708) CG6125 gene product [Droso...	330	3e-89
gi|7493011|pir||T39116 probable sulfate permease - fission yeas...	267	2e-70
gi|6094367|sp|O74377|SULH_SCHPO PROBABLE SULFATE PERMEASE SPBC3...	266	4e-70
gi|2626753|dbj|BAA23424.1| (AB008782) sulfate transporter [Arab...	266	4e-70
SPLICE FORM 2:		
gi|7302719|gb|AAF57797.1| (AE003802) CG5002 gene product [Droso...	404	e-111
gi|7301881|gb|AAF56989.1| (AE003772) CG7912 gene product [Droso...	394	e-108
gi|5834394|gb|AAD53951.1| (AF180728) sulfate transporter [Droso...	374	e-102
gi|7301216|gb|AAF56347.1| (AE003749) Esp gene product [Drosophi...	373	e-102
gi|7301962|gb|AAF57068.1| (AE003774) CG9702 gene product [Droso...	337	2e-91
gi|7294633|gb|AAF49971.1| (AE003543) CG6928 gene product [Droso...	332	6e-90
gi|7300023|gb|AAF55195.1| (AE003708) CG6125 gene product [Droso...	315	8e-85
gi|7493011|pir||T39116 probable sulfate permease - fission yeas...	254	2e-66
gi|9955547|emb|CAC05432.1| (AL391710) sulfate transporter [Arab...	254	2e-66
gi|2626753|dbj|BAA23424.1| (AB008782) sulfate transporter [Arab...	253	4e-66
gi|6502994|gb|AAF14540.1|AF163975_1 (AF163975) SutA [Penicilliu...	250	3e-65
gi|6094367|sp|O74377|SULH_SCHPO PROBABLE SULFATE PERMEASE SPBC3...	248	1e-64
gi|6502992|gb|AAF14539.1|AF163974_1 (AF163974) sulfate permease...	244	2e-63
gi|10645530|gb|AAG21641.1|AC069474_20 (AC069474) sulphate trans...	242	9e-63

BLAST to dbEST:
SPLICE FORM 1:

gb|AA582196.1|AA582196 nn44h12.s1 NCI_CGAP_GC5 Homo sapiens...	1027	0.0
gb|AI690196.1|AI690196 tx33c05.x1 NCI_CGAP_Lu24 Homo sapien...	948	0.0
gb|AI417381.1|AI417381 tg30c11.x1 NCI_CGAP_Brn25 Homo sapie...	902	0.0
gb|AW207633.1|AW207633 UI-H-BI1-af1-c-10-0-UI.s1 NCI_CGAP_S...	890	0.0
gb|AI494563.1|AI494563 qz16h03.x1 NCI_CGAP_CLL1 Homo sapien...	850	0.0
gb|H15131.1|H15131 ym30b04.s1 Soares infant brain 1NIB Homo...	805	0.0
gb|AI220943.1|AI220943 qg08c06.x1 Soares_placenta_8to9weeks...	743	0.0
gb|AW055140.1|AW055140 wz01c04.x1 NCI_CGAP_Brn23 Homo sapie...	718	0.0
gb|AI963799.1|AI963799 wr67b09.x1 NCI_CGAP_Ut1 Homo sapiens...	718	0.0
gb|N54913.1|N54913 yv34f02.s1 Soares fetal liver spleen 1NF...	710	0.0
gb|AW008673.1|AW008673 ws71c02.x1 NCI_CGAP_Brn23 Homo sapie...	688	0.0
gb|AI680222.1|AI680222 tw66e04.x1 NCI_CGAP_Ut3 Homo sapiens...	638	e-180
gb|AA385773.1|AA385773 EST99540 Thyroid Homo sapiens cDNA 5...	636	e-180
gb|H04038.1|H04038 yj45b06.r1 Soares placenta Nb2HP Homo sa...	626	e-177
gb|AI000592.1|AI000592 os63b01.s1 NCI_CGAP_Br2 Homo sapiens...	618	e-174

BLAST to CHGI:

TA_39934	NOT ASSIGNED [Homo sapiens]	1544	0.0
TA_44508	NOT ASSIGNED [Homo sapiens]	509	e-142
TA_102843	NOT ASSIGNED [Homo sapi...	484	e-135
TA_82272	AAD14 [Homo sapiens]	44	0.018
TA_71453	ataxin SCA1 [Homo sapiens]	44	0.018
TA_74619	alkaline phosphatase, pl...	42	0.070
TA_52146	NOT ASSIGNED [Homo sapiens]	42	0.070
TA_237492	NOT ASSIGNED [Homo sapi...	40	0.28
TA_158839	NOT ASSIGNED [Homo sapi...	40	0.28

EXPRESSION INFORMATION FOR MODULATORY USE:
SPLICE FORM 1:
Library source from BLAST dbEST hits:

AA582196 534 bp mRNA EST 05-SEP-1997 germ cell tumor
AI690196 486 bp mRNA EST 16-DEC-1999 carcinoid:lung
AI417381 470 bp mRNA EST 30-MAR-1999 anaplastic oligodendroglioma: brain
AW207633 511 bp mRNA EST 02-DEC-1999 unknown
AI494563 457 bp mRNA EST 17-MAR-1999 B-cell, chronic lymphotic leukemia
H15131 508 bp mRNA EST 27-JUN-1995 infant brain, 73 days post natal
AI220943 375 bp mRNA EST 29-NOV-1998 two placentae: one from 8 weeks and another from 9 weeks post conception
AW055140 366 bp mRNA EST 09-MAR-2000 glioblastoma (pooled): brain
AI963799 377 bp mRNA EST 08-MAR-2000 well-differentiated endometrial adenocarcinoma, 7 pooled tumors: uterus
N54913 486 bp mRNA EST 28-JAN-1997 fetal liver and spleen
AW008673 369 bp mRNA EST 10-SEP-1999 glioblastoma (pooled): brain

Library source from cDNA retrieval:
Human Fetal Brain
Human Brain
Human Pituitary Gland
Human Heart
Human Leukocytes
Human Kidney
Human Hela Cell
Human Liver
Human Thyroid
Human Lung
Human Placenta
Human Skeletal Muscle
Human Fetal Kidney
Human Small Intestine
Human Prostate
Human Testis
Human Adrenal Gland
Human Bone Marrow
Human Pancreas

SPLICE FORM 1:

```
       1  MPSSVTALGQ ARSSGPGMAP SACCCSPAAL QRRLPILAWL PSYSLQWLKM
      51  DFVAGLSVGL TAIPQALAYA EVAGLPPQYG LYSAFMGCFV YFFLGTSRDV
     101  TLGPTAIMSL LVSFYTFHEP AYAVLLAFLS GCIQLAMGVL RLGFLLDFIS
     151  YPVIKGFTSA AAVTIGFGQI KNLLGLQNIP RPFFLQVYHT FLRIAETRVG
     201  DAVLGLVCML LLLVLKLMRD HVPPVHPEMP PGVRLSRGLV WAATTARNAL
     251  VVSFAALVAY SFEVTGYQPF ILTGETAEGL PPVRIPPFSV TTANGTISFT
     301  EMVQDMGAGL AVVPLMGLLE SIAVAKAFAS QNNYRIDANQ ELLAIGLTNM
     351  LGSLVSSYPV TGSFGRTAVN AQSGVCTPAG GLVTGVLVLL SLDYLTSLFY
     401  YIPKSALAAV IIMAVAPLFD TKIFRTLWRV KRLDLLPLCV TFLLCFWEVQ
     451  YGILAGALVS LLMLLHSAAR PETKVSEGPV LVLQPASGLS FPAMEALREE
     501  ILSRALEVSP PRCLVLECTH VCSIDYTVVL GLGELLQDFQ KQGVALAFVG
     551  LQVPVLRVLL SADLKGFQYF STLEEAEKHL RQEPGTQPYN IREDSILDQK
     601  VALLKA (SEQ ID NO:3)
```

SPLICE FORM 2:

```
       1  MPSSVTALGQ ARSSGPGMAP SACCCSPAAL QRRLPILAWL PSYSLQWLKM
      51  DFVAGLSVGL TAIPQALAYA EVAGLPPQYG LYSAFMGCFV YFFLGTSRDV
     101  TLGPTAIMSL LVSFYTFHEP AYAVLLAFLS GCIQLAMGVL RLAHISPHPL
     151  GLGGAGTSSM SPLGWPGFLL DFISYPVIKG FTSAAAVTIG FGQIKNLLGL
     201  QNIPRPFFLQ VYHTFLRIAE TRVGDAVLGL VCMLLLLVLK LMRDHVPPVH
     251  PEMPPGVRLS RGLVWAATTA RNALVVSFAA LVAYSFEVTG YQPFILTGET
     301  AEGLPPVRIP PFSVTTANGT ISFTEMVQDM GAGLAVVPLM GLLESIAVAK
     351  AFASQNNYRI DANQELLAIG LTNMLGSLVS SYPVTGSFGR TAVNAQSGVC
     401  TPAGGLVTGV LVLLSLDYLT SLFYYIPKSA LAAVIIMAVA PLFDTKIFRT
     451  LWRVKRLDLL PLWVTFLLCF WEVQYGILAG ALVSLLMLLH SAARPETKVS
     501  EGPVLVLQPA SGLSFPAMEA LREEILSRAL EVSPPRCLVL ECTHVCSIDY
     551  TVVLGLGELL QDFQKQGVAL AFVGLQVPVL RVLLSADLKG FQYFSTLEEA
     601  EKHLRQEPGT QPYNIREDSI LDQKVALLKA (SEQ ID NO:4)
```

FEATURES:

Functional domains and key regions:

SPLICE FORM 1:

[1] PDOC00001 PS00001 ASN_GLYCOSYLATION
N-glycosylation site

	294-297 NGTI

[2] PDOC00005 PS00005 PKC_PHOSPHO_SITE
Protein kinase C phosphorylation site
Number of matches: 2

1	96-98	TSR
2	245-247	TAR

[3] PDOC00006 PS00006 CK2_PHOSPHO_SITE
Casein kinase II phosphorylation site
Number of matches: 6

1	96-99	TSRD
2	116-119	TFHE
3	298-301	SFTE
4	571-574	STLE
5	572-575	TLEE
6	595-598	SILD

[4] PDOC00008 PS00008 MYRISTYL
N-myristoylation site
Number of matches: 15

1	9-14	GQARSS
2	17-22	GMAPSA
3	55-60	GLSVGL
4	80-85	GLYSAF
5	168-173	GQIKNL
6	232-237	GVRLSR
7	238-243	GLVWAA
8	307-312	GAGLAV
9	317-322	GLLESI
10	352-357	GSLVSS
11	380-385	GGLVTG
12	381-386	GLVTGV
13	452-457	GILAGA
14	456-461	GALVSL
15	543-548	GVALAF

[5] PDOC00870 PS01130 SULFATE_TRANSP
Sulfate transporters signature
77-98 PQYGLYSAFMGCFVYFFLGTSR

Membrane spanning structure and domains:
SPLICE FORM 1:

Helix	Begin	End	Score	Certainty
1	11	31	0.878	Putative
2	50	70	1.193	Certain
3	77	97	1.866	Certain
4	120	140	1.767	Certain
5	148	168	1.097	Certain
6	199	219	1.547	Certain
7	247	267	1.151	Certain
8	283	303	0.683	Putative
9	306	326	1.282	Certain
10	342	362	1.277	Certain
11	372	392	1.695	Certain
12	401	421	1.366	Certain
13	449	469	1.784	Certain
14	477	497	0.915	Putative
15	542	562	0.834	Putative

```
BLAST Alignment to Top Hit:
SPLICE FORM 1:
gi|7302719|gb|AAF57797.1| (AE003802) CG5002 gene product [Droso...   418  e-116

Query: 25  CSPAALQRRLPILAWLPSYSLQWLKMDFVAGLSVGLTAIPQALAYAEVAGLPPQYGLYSA 84
           C P+ +  + PIL WLP Y L+++  DF+AG +VGLT IPQA+AY  VAGL PQYGLYSA
Sbjct: 28  CRPSTVTNKFPILKWLPRYRLEYIMQDFIAGFTVGLTTIPQAIAYGVVAGLEPQYGLYSA 87

Query: 85  FMGCFVYFFLGTSRDVTLGPTAIMSLLVSFYTFHEPAYAVLLAFLSGCIQLAMGVLRLGF 144
           FMGCF Y   G+ +DVT+  TAIM+L+V+ Y    P YAVL+ FL+GCI L +G+L +G
Sbjct: 88  FMGCFTYIVFGSCKDVTIATTAIMALMVNQYATISPDYAVLVCFLAGCIVLLLGLLNMGV 147

Query: 145 LLDFISYPVIKGFTSAAAVTIGFGQIKNLLGLQNIPRPFFLQVYHTFLRIAETRVGDAVL 204
           L+ FIS PVI GFT AAA TIG  QI N++GL +          + F  +   R+ DA+L
Sbjct: 148 LVRFISIPVITGFTMAAATTIGSAQINNIVGLTSPSNDLLPAWKNFFTHLTSIRLWDALL 207

Query: 205 GLVCMLLLLVLKLMRDHVPPVHPEMPPGVRLSRGLVWA-ATTARNALVVSFAALVAYSFE 263
           G+  ++ LL++  ++D            ++    + W     +RNAL V F   +AY
Sbjct: 208 GVSSLVFLLLMTRVKD------------IKWGNRIFWKYLGLSRNALAVIFGTFLAYILS 255

Query: 264 VTGYQPFILTGETAEGLPPVRIPPFSVTTANGTISFTEMVQDMGAGLAVVPLMGLLESIA 323
             G QPF +TG    G+PP R+PPFS T     +SF EM+  +GA L  +PL+ +LE +A
Sbjct: 256 RDGNQPFRVTGNITAGVPPFRLPPFSTTVDGEYVSFGEMISTVGASLGSIPLISILEIVA 315

Query: 324 VAKAFASQNNYRIDANQELLAIGLTNMLGSLVSSYPVTGSFGRTAVNAQSGVCTPAGGLV 383
           ++KAF+      +DA+QE++A+G+ N++GS V S PVTGSF RTAVN  SGV TP GG V
Sbjct: 316 ISKAFS--KGKIVDASQEMVALGMCNIMGSFVLSMPVTGSFTRTAVNNASGVKTPLGGAV 373

Query: 384 TGVLVLLSLDYLTSLFYYIPKSALAAVIIMAVAPLFDTKIFRTLWRVKRLDLLPLCVTFL 443
           TG LVL++L +LT  FY+IPK  LAA+II A+  L +    + +W+ K+ DL P  VT L
Sbjct: 374 TGALVLMALAFLTQTFYFIPKCTLAAIIIAAMISLVELHKIKDMWKSKKKDLFPFVVTVL 433

Query: 444 LC-FWEVQYGILAGALVSLLMLLHSAARPET-----KVSEGPVLVLQPASGLSFPAMEAL 497
            C FW ++YGIL G   +++ +L+S+ARP       K++   V V+     L + + E L
Sbjct: 434 TCMFWSLEYGILCGIGANMVYILYSSARPHVDIKLEKINGHEVSVVDVKQKLDYASAEYL 493

Query: 498 REEILSRAL--EVSPPRCLVLECTHVCSIDYTVVLGLGELLQDFQKQGVALAFVGLQVPV 555
           +E+++ R L  +    + +V++   + SIDYTV + +  +  D +    A+      +
Sbjct: 494 KEVLVNRFLNNQNGETQLVVIKGEEINSIDYTVAMNIVSMKGDLEALNCAMICWNWNIAS 552

Query: 556 LRVL--LSADLKG-FQYFSTLEE 575
             V+  L+ DL+  F++  +LEE
Sbjct: 553 AGVVCRLNNDLRPIFKFDLSLEE 575 (SEQ ID NO :6)


SPLICE FORM 2:
>gi|7302719|gb|AAF57797.1| (AE003802) CG5002 gene product
          [Drosophila melanogaster]
          Length = 595

 Score =  404 bits (1026), Expect = e-111
 Identities = 233/587 (39%), Positives = 340/587 (57%), Gaps = 51/587 (8%)

Query: 25  CSPAALQRRLPILAWLPSYSLQWLKMDFVAGLSVGLTAIPQALAYAEVAGLPPQYGLYSA 84
           C P+ +  + PIL WLP Y L+++  DF+AG +VGLT IPQA+AY  VAGL PQYGLYSA
Sbjct: 28  CRPSTVTNKFPILKWLPRYRLEYIMQDFIAGFTVGLTTIPQAIAYGVVAGLEPQYGLYSA 87

Query: 85  FMGCFVYFFLGTSRDVTLGPTAIMSLLVSFYTFHEPAYAVLLAFLSGCIQLAMGVLRLAH 144
           FMGCF Y   G+ +DVT+  TAIM+L+V+ Y    P YAVL+ FL+GCI L +G+L +
Sbjct: 88  FMGCFTYIVFGSCKDVTIATTAIMALMVNQYATISPDYAVLVCFLAGCIVLLLGLLNM-- 145

Query: 145 ISPHPLGLGGAGTSSMSPLGWPGFLLDFISYPVIKGFTSAAAVTIGFGQIKNLLGLQNIP 204
                          G L+ FIS PVI GFT AAA TIG  QI N++GL +
Sbjct: 146 ---------------GVLVRFISIPVITGFTMAAATTIGSAQINNIVGLTSPS 183

Query: 205 RPFFLQVYHTFLRIAETRVGDAVLGLVCMLLLLVLKLMRDHVPPVHPEMPPGVRLSRGLV 264
```

```
                 + F  +   R+ DA+LG+  ++ LL++  ++D            ++    +
Sbjct: 184 NDLLPAWKNFFTHLTSIRLWDALLGVSSLVFLLLMTRVKD----------IKWGNRIF 231

Query: 265 WA-ATTARNALVVSFAALVAYSFEVTGYQPFILTGETAEGLPPVRIPPFSVTTANGTISF 323
           W     +RNAL V F   +AY     G QPF +TG    G+PP R+PPFS T     +SF
Sbjct: 232 WKYLGLSRNALAVIFGTFLAYILSRDGNQPFRVTGNITAGVPPFRLPPFSTTVDGEYVSF 291

Query: 324 TEMVQDMGAGLAVVPLMGLLESIAVAKAFASQNNYRIDANQELLAIGLTNMLGSLVSSYP 383
            EM+  +GA L  +PL+ +LE +A++KAF+      +DA+QE++A+G+ N++GS V S P
Sbjct: 292 GEMISTVGASLGSIPLISILEIVAISKAFS--KGKIVDASQEMVALGMCNIMGSFVLSMP 349

Query: 384 VTGSFGRTAVNAQSGVCTPAGGLVTGVLVLLSLDYLTSLFYYIPKSALAAVIIMAVAPLF 443
           VTGSF RTAVN  SGV TP GG VTG LVL++L +LT  FY+IPK  LAA+II A+  L
Sbjct: 350 VTGSFTRTAVNNASGVKTPLGGAVTGALVLMALAFLTQTFYFIPKCTLAAIIIAAMISLV 409

Query: 444 DTKIFRTLWRVKRLDLLPLWVTFLLC-FWEVQYGILAGALVSLLMLLHSAARPET----- 497
           +    + +W+ K+ DL P  VT L C FW ++YGIL G   +++ +L+S+ARP
Sbjct: 410 ELHKIKDMWKSKKKDLFPFVVTVLTCMFWSLEYGILCGIGANMVYILYSSARPHVDIKLE 469

Query: 498 KVSEGPVLVLQPASGLSFPAMEALREEILSRAL--EVSPPRCLVLECTHVCSIDYTVVLG 555
           K++   V V+     L + + E L+E+++ R L  +    + +V++   + SIDYTV +
Sbjct: 470 KINGHEVSVVDVKQKLDYASAEYLKEKVV-RFLNNQNGETQLVVIKGEEINSIDYTVAMN 528

Query: 556 LGELLQDFQKQGVALAFVGLQVPVLRVL--LSADLKG-FQYFSTLEE 599
           +  +  D +    A+      +    V+  L+ DL+  F++  +EE
Sbjct: 529 IVSMKGDLEALNCAMICWNWNIASAGVVCRLNNDLRPIFKFDLSLEE 575 (SEQ ID NO :7)
```

Multiple sequence alignment of both splice forms and the top blast hit:

```
Splice Form 1 ~~~~~~~~~~ ~~MPSSVTAL GQARSSGPGM APSACCCSPA ALQRRLPILA
Splice Form 2 ~~~~~~~~~~ ~~MPSSVTAL GQARSSGPGM APSACCCSPA ALQRRLPILA
gi7302719_pe MRADEDNLYR EQLPNVSTLI ...RDGGRKL ......CRPS TVTNKFPILK

                51                                                100
Splice Form 1 WLPSYSLQWL KMDFVAGLSV GLTAIPQALA YAEVAGLPPQ YGLYSAFMGC
Splice Form 2 WLPSYSLQWL KMDFVAGLSV GLTAIPQALA YAEVAGLPPQ YGLYSAFMGC
gi7302719_pe WLPRYRLEYI MQDFIAGFTV GLTTIPQAIA YGVVAGLEPQ YGLYSAFMGC

                101                                               150
Splice Form 1 FVYFFLGTSR DVTLGPTAIM SLLVSFYTFH EPAYAVLLAF LSGCIQLAMG
Splice Form 2 FVYFFLGTSR DVTLGPTAIM SLLVSFYTFH EPAYAVLLAF LSGCIQLAMG
gi7302719_pe FTYIVFGSCK DVTIATTAIM ALMVNQYATI SPDYAVLVCF LAGCIVLLLG

                151                                               200
Splice Form 1 VLRL...... .......... ........GF LLDFISYPVI KGFTSAAAVT
Splice Form 2 VLRLAHISPH PLGLGGAGTS SMSPLGWPGF LLDFISYPVI KGFTSAAAVT
gi7302719_pe  LLNM...... .......... ........GV LVRFISIPVI TGFTMAAATT

                201                                               250
Splice Form 1 IGFGQIKNLL GLQNIPRPFF LQVYHTFL.R IAETRVGDAV LGLVCMLLLL
Splice Form 2 IGFGQIKNLL GLQNIPRPFF LQVYHTFL.R IAETRVGDAV LGLVCMLLLL
gi7302719_pe  IGSAQINNIV GLTS.PSNDL LPAWKNFFTH LTSIRLWDAL LGVSSLVFLL

                251                                               300
Splice Form 1 VLKLMRDHVP PVHPEMPPGV RLSRGLVWA. ATTARNALVV SFAALVAYSF
Splice Form 2 VLKLMRDHVP PVHPEMPPGV RLSRGLVWA. ATTARNALVV SFAALVAYSF
gi7302719_pe  LMTRVKD... .........I KWGNRIFWKY LGLSRNALAV IFGTFLAYIL
```

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                301                                                 350
Splice Form 1 EVTGYQPFIL TGETAEGLPP VRIPPFSVTT ANGTISFTEM VQDMGAGLAV
Splice Form 2 EVTGYQPFIL TGETAEGLPP VRIPPFSVTT ANGTISFTEM VQDMGAGLAV
gi7302719_pe  SRDGNQPFRV TGNITAGVPP FRLPPFSTTV DGEYVSFGEM ISTVGASLGS

                351                                                 400
Splice Form 1 VPLMGLLESI AVAKAFASQN NYRIDANQEL LAIGLTNMLG SLVSSYPVTG
Splice Form 2 VPLMGLLESI AVAKAFASQN NYRIDANQEL LAIGLTNMLG SLVSSYPVTG
gi7302719_pe  IPLISILEIV AISKAFS..K GKIVDASQEM VALGMCNIMG SFVLSMPVTG

                401                                                 450
Splice Form 1 SFGRTAVNAQ SGVCTPAGGL VTGVLVLLSL DYLTSLFYYI PKSALAAVII
Splice Form 2 SFGRTAVNAQ SGVCTPAGGL VTGVLVLLSL DYLTSLFYYI PKSALAAVII
gi7302719_pe  SFTRTAVNNA SGVKTPLGGA VTGALVLMAL AFLTQTFYFI PKCTLAAIII

                451                                                 500
Splice Form 1 MAVAPLFDTK IFRTLWRVKR LDLLPLCVTF LLC.FWEVQY GILAGALVSL
Splice Form 2 MAVAPLFDTK IFRTLWRVKR LDLLPLWVTF LLC.FWEVQY GILAGALVSL
gi7302719_pe  AAMISLVELH KIKDMWKSKK KDLFPFVVTV LTCMFWSLEY GILCGIGANM

                501                                                 550
Splice Form 1 LMLLHSAARP ET.....KVS EGPVLVLQPA SGLSFPAMEA LREEILSRAL
Splice Form 2 LMLLHSAARP ET.....KVS EGPVLVLQPA SGLSFPAMEA LREEILSRAL
gi7302719_pe  VYILYSSARP HVDIKLEKIN GHEVSVVDVK QKLDYASAEY LKEKVV.RFL

                551                                                 600
Splice Form 1 ..EVSPPRCL VLECTHVCSI DYTVVLGLGE LLQDFQKQGV ALAFVGLQVP
Splice Form 2 ..EVSPPRCL VLECTHVCSI DYTVVLGLGE LLQDFQKQGV ALAFVGLQVP
gi7302719_pe  NNQNGETQLV VIKGEEINSI DYTVAMNIVS MKGDLEALNC AMICWNWNIA

                601                                                 650
Splice Form 1 VLRVL..LSA DLKG.FQYFS TLEEAEKHLR QEPGTQPYNI REDSILDQKV
Splice Form 2 VLRVL..LSA DLKG.FQYFS TLEEAEKHLR QEPGTQPYNI REDSILDQKV
gi7302719_pe  SAGVVCRLNN DLRPIFKFDL SLEEVVAGHF DSPSNTASTV TIEA~~~~~~

                651
Splice Form 1 ALLKA
Splice Form 2 ALLKA
gi7302719_pe  ~~~~~
```

Hmmer search results (Pfam):

Model	Seq-from	Seq-to	HMM-from	HMM-to	Score	E-value	Description
Sulfate_transp family	137	468	1	328	229.9	1.3e-66	Sulfate transporter

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   1  GGTCCCCGCG GCCCTCGGCC TTGCTCGGGG CCAAGGGACC GCGGACGGTC
  51  AGGTGGCGCA GGGTCTCCTC CGGAGACCCC AGGATCCGGA GCCAGCGGCC
 101  TTGTGGGCAG GGGCCGGGGG CAGGGGAGTG GATTTTGCCC GGAGCGGAGC
 151  AGGCCGGGGG CAGTGGGGGG CTGGGGGTGA GGGTGGCTGG CTCTGCGCGC
 201  GGGCGCCGGG GCCCTGGAAG ATGCTGCGCA CCTGAATTAA CCGGGCGCCT
 251  CTGATGTCCT CCCAGAAGCA ACTAGAACTC CAGGGCTGTG AAAGCCACAG
 301  GTGGGGGCTG AGCGAGGCTT GGCCTCAGGA GCGGAGGACC CCCCCCCCCC
 351  CCCCCTCGAG CGCCGCAGTC CACCGTAGCG GGTGGAGCCC GCCTTGGTGC
 401  GCAGTTGGAA AACCTCGGAA GCCCCGCTGG ATCTCCTGGC TGCCACCCGC
 451  ACCCCCCGCC AGCTACGGTG CGCCCGCGGG CCCAGCTTCT CTCTGCGCTG
 501  CTCCCCGTTA AATTCCCTGG GGAGACGGAA AAAAAGGCAA AGGAAGTCGG
 551  TTCTCCAGGG GCCAGAAGTG TTGAGCCTAA TTAGTCTTCA GACTTCTCAA
 601  TGAGGAATCG CTTATCAGTT TCTTATCTGG GAGAGTTGAG GATGGAGGGA
 651  CAGAAGGCAC CCAGGATTTG CACGGGGGGG GATTCAGGGA GAGAGGGTGA
 701  TGAGGGACGG GGTGGGCCTT CCAGTCTTGG CCCAGTCCCC ATCTTGCACA
 751  CATTGTTGGC TTCCTCTTAG AGCCGTTCGC CCCCCTGGGG AGGGGAGACC
 801  CATAGTGACC TCTCCTGACA CCCGCCGACC CTGACCAGTG TTGCCGGGTT
 851  CTTCAAAGGC CACGCTCTGA CTGCTGGTCT GTGTCACCTG CACCCCCCAG
 901  CCCCACCGTA GAGATGCCTT CTTCGGTGAC GGCGCTGGGT CAGGCCAGGT
 951  CCTCTGGCCC CGGGATGGCC CCGAGCGCCT GCTGCTGCTC CCCTGCGGCC
1001  CTGCAGAGGA GGCTGCCCAT CCTGGCGTGG CTGCCCAGCT ACTCCCTGCA
1051  GTGGCTGAAG ATGGATTTCG TCGCCGGCCT CTCAGTTGGC CTCACTGCCA
1101  TTCCCCAGGC GCTGGCCTAT GCTGAAGTGG CTGGACTCCC GCCCCAGGTG
1151  AGGCGTCTGA CCCTGCTGCC AGCCATATCT CAGAAACAGT GCAGAATACA
1201  CAGTATCAAT CCCAGACACC ATCAGCGATT CCAGGTTTCC AGCCCCTGGG
1251  CCCCAAGGAA CCTTTGGTTT ACAGTGTGTG ACGCAGATTG TCTCTGGGCC
1301  GACCCAGGCT CCTATGCCTG TTTGGTACAC ACAGACACTG AGCTGGTTAT
1351  GGAGGGGCCA GCGAGATGAC TCATGGAGGC CTCAGGAGTT CAAGACCAGC
1401  CCGACCAAAA TGGTGAAACC CCGTCTCCAC TAAAAATACA AAAATTAGGC
1451  TGGGTGCGGT GGCTCAAGCC TGTAATCCCA GCACTTTGGG AGGCCGAGGC
1501  AGGCGGATCG CAAGGTCAGG AGATGGAGAC CATCCTGGCT AACAGGGTGA
1551  AACCCCGTCT CTACTAAAAA TACAAAAAAT TAGCCAGGTG TGGTGGCGGG
1601  TGCCTGTAGT CCCAGCTACC TGGGAGGCTG AGGCAGGAGA ATGGCGTGAA
1651  CCCGGGAGGC GGAGCTTGCA GTGAGCCGAG ACTGTGCCAC TGCCCTCCAG
1701  CCTGGGCGAC AGAGCGAGAC TCCATCTCAA AAAAAAAAAA AAAAGAATGC
1751  TTCCTCAGAC TTGGACACAG CACACGGGCC TGTACCGACC CCTCTGCCTG
1801  GCTGTCTGCA CCCTGAGGCC CCAGTTGAGT GCTGCTAAAA AAGTGGCCTC
1851  CTGATCACTG CAGGTCCACC CACAGGGCAG GGCGGTGCAC CTTTAACCTG
1901  GGCCTGGACA CAGCTGACAC CCACACATCC CGAGCTTGGA CACGCACACT
1951  AGGGAGCTGG TGGATGGGCC TCGGCCTCCT GAGTGCTCAC CACCCTCTCT
2001  CCCCACAGTA TGGCCTCTAC TCTGCCTTCA TGGGCTGCTT CGTGTATTTC
2051  TTCCTGGGCA CCTCCCGGGA TGTGACTCTG GGCCCCACCG CCATTATGTC
2101  CCTCCTGGTC TCCTTCTACA CCTTCCATGA GCCCGCCTAC GCTGTGCTGC
2151  TGGCCTTCCT GTCCGGCTGC ATCCAGCTGG CCATGGGGGT CCTGCGTTTG
2201  GGTGAGGCTC TACCTTCTTG CCAAGGGGAT GCCCTCGACC TCAGCATTTG
2251  CTTGTTTGCA TTTCAAGTCT ATCCCCGTGT GCGTGTGTGT GCGTGTTGTG
2301  GGGGTGTGGG TATGTATGTG TGTGTGTGTA GGTGGGTGGG TGGTGGAGGG
2351  GGTGGGGCAC TTGGCTCCTT AGTCTACTAT TTTACTGATT AGAGGCCAGG
2401  ACATTGGAGA AAGTGACCTG TGGCTCAGAC CCCATATGCC CCNNNNNNNN
2451  NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNTTCATTTC
2501  CTACCCCGTC ATTAAAGCTT CACCTCTGCT GCTGCCGTCA CCATCGGCTT
2551  TGGACAGATC AAGGTAGGCA CGGCGCCCAC CCAGGGCACT GCTCTTTGGC
2601  CACTGCTCGT TGGCACAGGG ATGGCGGGAG CAGGACTGAG GCCAGTCCTG
2651  ATCCCTGTGG CCAGTGGACG TCTTGCTGTT TCAGATTGTC TTCCATGGGT
2701  CAAGAAGCAC GCGGTGCTCT CATGGGTCCC CTGTTAATAA AATGACCCTC
2751  CTGGGAGGGA TGTCACGTGA TGGTTGGATT TCACAGCGGG TAACTTGGGG
2801  GCCGGTAATT CCATCCCCCT GCTCTTGCCC GAGTTCCGT GCCAGTGTGC
2851  TTGGCTGGCT CTGTGACGTG GCTCTGTTCT CCCTGCACTG GGCACACCCA
2901  GCAGGCCCCA CCAGTCATGA GCATGCTGCT AGAATTTCTA TAGGCAAATT
2951  ATTTCCCCAT GCCAATTTAG TTAGATGGTT TTGTTTTGTG CTTTTTTTTC
3001  TGGTTTCTGT TTAATATTTT TTAAATGCCA TGCCTTTTAT ATTTTCTTTT
3051  AAAACATTTA TAATAAGTAC TAAAATCAGT CATCAGCTGA GGGTGTAATT
3101  TATTCTGTTT TTGCTGGGTT GTAAGTTCCT CGAGGGTAGG AACTGTCCTT
3151  CTCCCAGCCA TGGCCGCCCA GCATTGGGCT GGTGCAGTAG GGGGGTGCTC
3201  AGTGGGGTGT GTGTGGAGTG AAGTGAGCCC AGTTCCACAG ATGGGACCAT
3251  GCGGCCCTCA TGGCAGACTA GGGTCACATG CTGCCTCCTG ACCCTGTGTC
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3301  ACTGCAGGTC ATCTTCCCCA AGCCAGGCCC TGTTCCAGGC TGGCCTGAGA
3351  CAGTCTTCCC TGATGGAGGT ACCATGAGAA GACCAAGGAC AGGAGAGTGT
3401  GTGTGAGAGT GTGTATGAGT GTGTGTGTGT GTGAATGAGT GAGTGTGTGA
3451  GAGTGTGAGT GGGTTTGAGG GAGTGAGTGT GTGCGTGTGT GAGTGAGTGT
3501  GAGTGTGGGT GTGAGTGAGT GCGTGTGTGT GAGAGAGTGT GTGAGTGTGT
3551  ATGAGTGAGA GTGTGAGAGT GGGTGTGGGT GTTAGGGAGT GTGTGAGTGT
3601  GCGCGCGCGT GTGTGAGTGT ATGAGTGTGA GAGTGAGTGT GAGTGAGTGA
3651  GAGTGGGTGT GGGTGTGAGT GTGCGTGTGA GTGTGAGAGT GTGAGTGTGT
3701  GAGTGTGAGA ATAAAGTAGA CACTTTTTGC ACTCTTGCTA CGTGCGAGGC
3751  ACTGGGCAGG ACACTCTCCA TGTGTAATTC TCAACACACC CCGGGAGGTA
3801  GATTTATCAT TATTTCCATT TGAGAGAGGA GGGACCAACT TAGGTGTGGG
3851  TGAGCGTGAT TTGTACGTTA TCTACACGCA TCTCTCAGGG TTAGCTTGGC
3901  AAATGCTGTT TCAGGGCATG GTTGGTTCTT TAATCTGGAA ACATCATTTT
3951  TGGTGTCAAG AATGTTCTTT TGTAGGATCC CAGTGAGAGT GGAGAGCGGA
4001  GAGTGGAGAG TGGAAGGCAT CCCTTGTTCA TGCCTTCATA CTTGGCAACC
4051  CTAGCCCCGC CCAGGGACTC TGCAGCCATC TGGGGGGAGG GGCGTCCTCC
4101  TGACAGGCCC AGGACAGAAG ACCCTACCCC AACAGTCCCA GAGTCCGCCC
4151  CCCAGGATGT CCTAACCCCA CCCACCCTGT ACGCAGCAGT TTTAGGGCAG
4201  GGTCCTTGAG CCTGTGGCCA TGGGATCCAG GGCCTCAACT TTCCCCTCTG
4251  ACTCCTGTTG GGTCTCAGGC GATGTAAAGA ACTAAAGTGC AAGCTGTGCC
4301  TGCACTGTGG ATCCCAGCTA CGTGGGAGGC CGAGGTGGGA GGATCACTGG
4351  AGCCCAGGAG TTCGAATCCA GCCTGGGCCA CAGAGCAAGC AAGACCCCCA
4401  CCCCCCAACC CCCCGCCGCT CTCTAAAGAA AAAAAAACTA AACTAAAACA
4451  CAGGATAGAG TGCCTTCTCC TGCCCAGGAC CTCAGAGCTG GTATCGTGGT
4501  GGGAGGCTCC TACTTTGCCG AGGATTCCCC AAGCTGGTTT CTTGAAGCCC
4551  CTCAGAGCCC TCCACATCTG CACACTACGA AGAGATTTTT CCTCCCGCAG
4601  CAGCGGAGCT GGGGGGTGGC GGGGCACCTA GTGAGGGAGA CATTCTCAAG
4651  CCAATGGCAG CAAGGGTCTA CACTGCAGGG GGCCTGGCTG CTGAGTGGCC
4701  TGGAGCCAAT GGGGGTGGGG CCAGGCAGCC CATGGCCCCT GGCCATCAAG
4751  CTGTAGAACC TGTCTGCCTG CTGTGGGGTC ACCTACATTG TTTTTTATGA
4801  GAAAAGTAAT TTAGAGAAAA ACATATCACT GACCCAGTAA TTGTGAAGTA
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4901  GTGGGCAGGT GGACCCCTGA GCCCCTAAGA TGGGCCCCGG GAATAAGGGT
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5001  GAGCTGGGGA CAGATGGCCT TGGTTTGGGA GCATAGCCTC TGATCAGCAT
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5101  TCTTCCTGCA GGTGTACCAC ACCTTCCTCA GGATTGCAGA GACCAGGTAC
5151  CCCGGGCTTT GTTCCTCCCT CCTATAAGGA AGCTCCTTCT TCCACACCTC
5201  CTCTCCCGGC CCCCACCTCA GTTTCCCCAC CCCTGGTGAC TGCTCAAACA
5251  GGGGTCCCCA GAGCAGCCCC ATCAGCAGCA CCTGCAAGCT GGCAAGAAAT
5301  GAGACTCTCA GTCCTTTGCA GACCTGCCCT ATCGGAGCCA GAGGTTTAAC
5351  AGGAGGCCGG TGGTCTGCGC GCAGGGGAGA GTTCAAGAAG CTCTGCTCTG
5401  GGGAGCTGGA GCAGGGCAAT GTTCCTCTCT CCACAAAGCT TTCTTGGGGG
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5501  CCAGGCTGTG ATTTGTTAAG GAGGAGAACA CAGGGCGTGG GGAGCTAACC
5551  CAGACAGAAC GCAGGTGGTG CAGGGACGGC AGGTGGAGCT GTGATGAGAG
5601  ATGAGGAGAC CCAAGCACTT CCCTCAGGTG GTTTAAAGAG CCTCTGATGG
5651  CCGGACACTG TGGCTCACAC CTGTAATCCC AGCACTTTGG GAAGCCCAGG
5701  TGGGCAGATC ATCTTAGGTC AGGAGTTCAA GACCAGCCTG GTCAACATGG
5751  TGAAACTCCG TCTCTACTAA AAATACAAAA ATTAGTCGGG TGTGATGGTG
5801  CGTGCCTGTA GTCCCAGCTG TTCAGGAGGC TGAGGCAGGA GGATTGCTTG
5851  AACCTGTGAG GCGGAGGTTG CAGTGAGCTG AGATCACGCC ACTGCACTCC
5901  AGCCCGGGTG ATAGAGTGAG ACTCCATCTC CGCCCTGCCC TGCCCCCCCG
5951  AAAAGAAAAG CCTCTGATGA GGGGTACCTC CCTGCCAGAC CATCCAGCGG
6001  GAAGGCAGGA TGCCTCTCTA CCTCTCTGGC TGGAAGGGGC TGGAGGAGGA
6051  AATGATCTAG GGGAGCTATA GAGATGGCTG CCCAGTGCTG TGGCCTGGAG
6101  GGAGTGGGGG CGATCCTGGA CCATCTTCCC CTCCCCTCTG ATCTGCTGCC
6151  GAAGCTTCCC AGCAGCTGAA CCCAGCTGGA AGCCAGTGGG TTCTTTGCTC
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6401  CTAATGATAG CTGATGAGCT ACAAAAAAAT CATTGAAAGA ACTCATAATG
6451  TTTTAAGAAA GTTTACAAAT TTGTGTTGGG CCACATTCAA AGCCATCCCA
6501  GGCTGCACAT GGCCCACAGG CTGTGGGTTT GGCAGACTTG TTCTAGAGCC
6551  ACCTGCAGAG AGCATCAGCT GCTCAGGCTG GTCCCCATTC CCTGTGGTCA
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6651  AAAATGTGAG CACGTCGCTC TGCCATCATC ATGACCCGGG CCTCTCCACT
6701  GCCTGTCCTG CCCAAGCCTG TGTACTTACT GAATTTTGAA TTGAGTTTTG
6751  AAGTAGAACA GGGATGCATA TTGCTTAGGA GAAAACATCT CAGCCTAGTC
6801  TGTGTTTGGT CTTGCAGAGT AGCTTGCTAA AGTTCCTGAG CTTTAGTTAA
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7201  TCTGGCTGAC ATCGTATGCA ACCTTGGCTG CAGGTTGGGG TCACTTGGGG
7251  AGTCCTAGTC CCACCCTAGG GATTCTCACG TCATTGGTCT GGGTGTCACT
7301  TGAGCATTGG GACATTTAAA ACACCACACC AAACTCTGGG ACATGTACTT
7351  TTTATTTAAT TAATTAATTA ATTATTTTTT GAGACAGAGT TTCGCTCTGT
7401  CGCCCAGGCT GGAGTACAGT GGTGTGATAT TGGCTCACTG CAACCTCCGC
7451  CTCCCAGGTT CATGTGATTC TCCTGCCTCA GCCTCCTGAG TAGCTGGGAT
7501  TACAGGCGCA TGCCACCACG CTCGACTGAT TTTTGTATTT ATAGTAGAGA
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7601  GATCTGCCTG CCTCGGCCTC CCGAAGTGCT GGGATTACAG GCATGAGCCA
7651  CCGCCCCGAC CCAAACTCTA GAACATTTAA AACTCTGAGC CAAACTCGGT
7701  GGGTTCTGAT GCAGGGTCAG AGCTGAGAAC TGATGCATGG CCAGCTGTGG
7751  CCGTTCTCAA CCTGAAGCAG TTTTGCCCCC CTGGTGACAT GTGGCAATGT
7801  TGGGAAACAT TTTTGGTGGA TACCACCGGG CGAGGCAGTT GCTGGCAACT
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8051  CTTCAGGCGC GGAGGCTGCA GGCTGAGCCA CAACCAACCA GGGGTCCTTT
8101  GAGAAAGGGG TGGTGAGGGC TGCGTCGTGG AGGAGCAGGG CTGTCAGCAG
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8351  TTGGGGGCTG CAAAATCCAA CAGCCACAGA AGAGAGAGGG TGGCTGGATT
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8451  TCTCCCTGGA TCCTGTTCAG CAGACTTGAG GCCGTGGTGA ACACTGAGAG
8501  TCTGGTGGGG TGCAGAGGAT GCTGGGTTTA GAGTGGAGAT GTCCAGCTTC
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8601  CTGAGCTTTA GTTCAGTTGT CCGTGAAATA GTGAAAATGC TTTGTTATCT
8651  TTGTTATCTT TTGTTTTTTG TTTTTTTTTG GAGACGGTGT CTCACTCCTG
8701  TTGCCCAGGC TGGAGTGCAC TGGCCGTGAT CCTTGGCTCA CTGCAACCTG
8751  CCTCCTGGTT TTCAAGCAAT TATTCCCCCC TTAACCCTCC CGGAGTAGCC
8801  TGGGATTTAC AGGCCGTGCA CCCACCACAC CCGGGCTAAT TTTTTGTATT
8851  TTTGAGTTCA AGATGGGGGT TTCACCATTG TTGGCCCATG CTGGGTCTCG
8901  AAACTCCCNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN
8951  NNNNNNNNCC CTAACCCTGA AAGGCAGTGT CTCCGCAGCC AGAAAGGTCT
9001  TTTAAGATGT TTAGACATCG GTAATGTCCA GAAACTTCAG AAACATTTTA
9051  CAGTGTAGGG CTGCTGACTC CTTTCTCCCC AGTGTGTGTA GCATTGTCTT
9101  AGGAAACTAC TTAAAAAGCT TTTGATTCTT ATAACAGCTT TGAGAATGAG
9151  TTTATTATTT TTTCCATTTT GTCAGTGAGG AAAGTGAGCC TATGAAAGAT
9201  GAAAAATAAA ACAGAACTTC TCAAGGCCAC ACGACTGGGA AGAGGCAGAA
9251  CAAGGACTTC ACCCGAGTCG TCTGTCTTTT TTTCTGAATG GTCTGTCTAG
9301  AAGTGTGTCA ATGTTATGAT CCTCTCAAAG AACCAGCTTT TGGTTTCATT
9351  GATCTCCCTT TTGCTTTGGT TTTCTAGTTC ATTGATTTCT GCTTGGGCCT
9401  TTATTATTTC CTTTCTTCTA TTTATTTTCA GTTAACTTTA TCCTTTTTTT
9451  TTTTTTTTTC AAAAAAAAAT TTTTTTTTTT GAGACGGAGT TTCGCTCTTG
9501  TCCCCCAGGT TGGAGTGCAA TGGTGTGATC TCAGCTCACT GCAACCTCCG
9551  CCTCCCGGGT TCAAGTGATT CTCCTGCCTC AGCCTCCCAA GTAGCTGGGA
9601  TTACAGGCGT ATGCCACCAT GCCTGGCTAA TTTTTTGTAT TTTTAATAGA
9651  GACGGGGTTT CACCATGTTG GCCAGGCTGG TCTCGAACTC CTGAACTCAG
9701  GTGATCCACC CGCCTCAGCC TCCCAAAGTG CTGGGATTAC AGGCGTGAGC
9751  CACTGTGCCC GGCCTTTTTT TTCAGATTCT TAAGGTGGAA GCCTGGGTCT
9801  TTGATTTGAG ACCTTTCTTC TTTTCTAATA TGGTTGTTTA AATGCTGTAA
9851  ATTTCACTCC TAGCATTACT TTAGCTGCAT CCCACAGTTT TTATATATAT
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 9901  GCTGTTCTTT AATTTTTATT CGGTTCTAAA TACTTTGTGA TTTCCATTTT
 9951  GACTTCTCCT TTGACCTGTG GATTATTTAG AAGTGGATTA TATGATTTCT
10001  TCTGTGAAGC ATGGGAGTTA TTTAGTTTCC AAATAGTTGG GGGTTTCCCA
10051  ATTAGTACTT TGCCATTGAT TTCTAATTTA GTTCCATTGT GATAAGAAAA
10101  CGTACTTAGT GATTTAAATC TGTTTTCCTT TATTGAGAGT TGTATTATGG
10151  CCCTGAATAT GGTCTATCTT AGTGAATATT CTGTGTGTGC TTGAGAACAT
10201  GTTTTCTGCC ATTATTGGGT GGAATGTTCT GTAAATGTCA GTTAGGTCTG
10251  GTTGGTTATC TCAGGCTACT ATATTCTTGC TGATTTTCTT TCTACTTGTT
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24151  CCGGTCCCCT GCAGCACGCT AGGTTGGGTG GGGGCTTCCC GCTTGGGACA
24201  GGCCAAGCCT GGTGGAGGCC ACCCGGTCAG ACCCGCCTCC AGGACTCACT
24251  CCTCCCCACA GGTGTCAGAG GGGCCGGTTC TGGTCCTGCA GCCGGCCAGC
24301  GGCCTGTCCT TCCCTGCCAT GGAGGCTCTG CGGGAGGAGA TCCTAAGCCG
24351  GGCCCTGGAA GGTGCATGGG CGGGGGTCAA GGTGGTCTGA GGTCACTCCC
24401  CTGTCCTCTG CCCCCCACTC CCTGCTGTTC AGGACCCCAA GACCCTGTCC
24451  CCGACGCTCT CCAGTCCACA AGGATGCAGG CATCTCTGAG TGGGCTGGAC
24501  CGTCCTCTGT GGGCCTCAGC CAGTGGCTGC TGCAGCAAGG GTGGTGGCTC
24551  CCCACATATC ACTCCTTCCC TGCCCCTAAA GTCCGGTTCC TGTTTCTGGG
24601  GGGTTGATTT TAGGGGAGCT AAGGGCCTGT GAGTCCTAGG AGGGAAACAG
24651  CTGCTGCTGT CACCAAACAA TTGTCTCTGG TCCTGCCACC CGAATCCCCC
24701  AACTGGGCGA CTCAGCCGCC ACGAGATGGA GCACTCTGGC CTCTCTGTCC
24751  CCTGCCCCTG GCCAGAGCCT CCTTTGGCCT CTGCAGAGCA GCTTTGGGCT
24801  GCTCTGGGTG GCGTGACCTG GCTCGGGCCT GTCTCCCCAG TGTCCCCGCC
24851  ACGCTGCCTG GTCCTGGAGT GCACCCATGT CTGCAGCATC GACTACACTG
24901  TGGTGCTGGG ACTCGGCGAG CTCCTCCAGG ACTTCCAGAA GCAGGGCGTC
24951  GCCCTGGCCT TTGTGGGCCT GCAGGTGGGT GTGCACTGGG ATGCCTTAGG
25001  GGTTAGCAGC TGCCGGAAGG CCTTCCTGTG CCTGCCTCCC ATGGCGAATG
25051  TGACATCTCT GGGCTGTGAT GCTGGACGGC CCTTCGGCCG GTGCTGGCTC
25101  TGCTTCTGAT TTAAACAGTT CTTGTCCCCA TCTGGCCTTC CTCGTCCCTC
25151  CCTGTGGAAG GGGGAGCGGT GGCCCCCAGC CCTCCGAGGG GTCACGTTAT
25201  GGCTTCTGGT CACTGCCACA CTGTCCTTTG TGCTGGGGAC ACACAGTGAA
25251  CGAGGGTCAG TCCCTGCTCT CAGGGGAATT GTATTTTAGG AAACAAAAAG
25301  AGACAGGTGA GGCTAGGCGT GGTGGCACAC TCCTGGAATC CCAGCACTTT
25351  GGGAGGCCAA GGCGGGCAGA TCACCTGAGG TCAGGAGTTC AAGACCAGCC
25401  TGGCCAACAT GGTGAAACCC CGTCTCTACT AAAAATACAA AAAAAACTAG
25451  TCAGGTGTGG TGGCGAGCGC CTGTAATTCC AGCTACATGG GAGGCTGGGA
25501  GAATCGCTTG AACCTGGGAG GTGGAGGTTG CAGTAAGCCG AGATCCCACT
25551  ACTGTACTCC AGCCTGGGCG ACAGAGTGGG ACTCCATCTC AAAAACAAAC
25601  AAACGAAAAA AAACAGGTGC TCATAGAATT TCATGAAAAA CGTATTGTCA
25651  GGGCTTCCAG AGGCTGAAGA CGGGTTTCTA TGGAGGCCGT CCTGTTCAGA
25701  GCCGCAGGTA AAGTGTAAGG GCTGGGTCCC AGGCCCTGCG TCTTAGGCCT
25751  CACCTAGGAG CCTTCTGAGC ACTGCAGGGT CAACATCCCA GGGGTGTGGC
25801  CAGTGTTTGC AGAGAGGCAG GGGTCTCTGT TGCTGTGGTT AAATGTGCGC
25851  TCTCTGCCAA GTCCTAGATG GCAGAACGTG GGGGACTAGG GCGTGTCCCC
25901  AGGCGCCCAG AGGAGACATT CATGAACTAG CCATGGAACA GGAGGCCAAG
25951  TGACCCGTAT ACCCCAGGTG TGGACCACAG CCGACCCTTG TCAGAGTTTC
26001  CTTCATTCCC AACCTGGCCC ACGAGGCTAG TGTTATCTTC ATCCCCATGT
26051  CCAGAAGAGG TCACTGAGGC CCAGAGAAGC CAGGTAATCT GCCCACGGTC
26101  ACACAGGATG GTGGGCCCAG CTTCAGATTT GGGCATGTGC CTTCAGAACT
26151  TCGCTCATAA GTGTTACGTC CTGTGTCATA TTTGCAGAGC ACATGTCTTC
26201  ATGGTCTTTG GAGATGATTC ACTTAAAAAA ATACTCCTCT GACCCAGACA
26251  TGGTGGCTCA CACCTGTAAT CCCAGCACTT TGAGAGGCCG AGGCGGGAGG
26301  TCAAGGGTTT GAGACCAGCC TGGCCAACAT AGTGAAACTC CGTCTCTACT
26351  AAAAATACAA AAATTAGACG GGCATGGTGG CGCACGCCTG TAATCCCAGC
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26401  TGCTCAGGGG GCTGAGGCAG GAGAATCGCT TGAACCCGGG AGGCAGAGGT
26451  TGCAGTGAGC CGAGATCGCG CCATTGCACT CCAGCCTGGG TAACAAGAGT
26501  GAAACTCCAT CTCAAAAACA AACAAACAAA CAAACAAAAA GTCCTCTGGG
26551  CCAGGCGCTG TGGCTCACAC CTGTAATCCC AGCACTTTGG GAGGCCGAGG
26601  TAGGAGGATC ATTTGAGGCC AGGAGTTTGA GACCAGCCTG GGCAACATGA
26651  CGAAACCCCA TCAAAAAAAT AGGAAAAAAT AGCTGGACGT GGTGGTGTGC
26701  ACCTGTAGCT ACTCAGGAGG CTGAGGTGGG AGGATCACTT GAGTCTGGGA
26751  GGTTGAGGCT GCAGTGAGCC ATGATCGTGC CACTGCACTC CAGCCTGAGC
26801  AATGAGCAAG ACCCTGTCTC AAAAAACAAA AAATTTAAAA AAAAAAAATC
26851  TTCCTCTGAC AGCATTCCCC TGGGGCTGCG TTTCTTCTCA CCATTCACTG
26901  GTATGGAGGT GAAGCCATAC CTCTCCGGGA GACTCTGAGA TGGCATGTCT
26951  ACCAGGCTGC CGACCCGTGT GCTACAGAGG AACATCCCTG CCCTGGCTAA
27001  AGTCTGTCTG TCTCTCAGGT CCCCGTTCTC CGTGTCCTGC TGTCCGCTGA
27051  CCTGAAGGGG TTCCAGTACT TCTCTACCCT GGAAGAAGCA GGTGGGCACA
27101  GTCAGACATC CTGTGGCTTT GGTGATTTTG TAAAAATCAT AAATGCTTAT
27151  TGTAAAAAAT ATGGGAAACC AGCTGGGCAC AGTGGCTCAT GCCTGTAATC
27201  CCAGCACTTT GGGAGGCCGA GGCAGGTGGA TCACCTGAGG TCAGGAGTTC
27251  GAGACCAGCC TGGCCAACAT GGTAAAACCT CATCAGTACT AAAAATACAA
27301  AAATTAGCTG GGTGTGGTGG CATGCACCTC TAGTCCCAGC TATTCGGGAG
27351  GCTGAAGCAG CAGAATCGCT TGAACCCAGG AGGCAGAGGT TGCACTGAGC
27401  CGAGATTGTG CCTCTGCACT TCCAGAGTAG GGTGAGAGAG CTAGCCATGT
27451  TGTCCAGAAA ANNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN
27501  NNNNNNNNNN NCCTGGTTGA GCAGGTATAA TCGCTTGCAA CCCAGGTAGC
27551  AGCAGTTGTA CTGAGTCCGA GAATTGTGCC ACTGCACTCC AGCCTGGGTG
27601  AGAGCAGCGA GTACTCTGTC TCAAAAAAAA AAAAAACAAA AAAAACAGGA
27651  AACCACCTCC ACCCCAGTCC ACTTTGGTGA TCACTCCATA CCCCTCCCCT
27701  AAACACGCAT ATGTACCTGC CTGTCAGGAT GTGGATATAT GTTTGCGGTT
27751  TTACGTAAAT GGGACCATTT CATACCTGGT GCTCTGGAAC CCACATTTTT
27801  CATGCAGAAG GTTGGAAGGA TGTCCTTCCA GCCGAAAGTC CACATCCCGG
27851  GGGATCAGGA CAGAGCAGGG CCGGGTCAGG AGATCCAGAA GCCCCGGGAC
27901  AGAAGGTACG GGAGGGACAG GAGCAGGGTG GGCGCTGACC CTTGAGACAG
27951  CAATCGCAGG AGGTCTGAGC CGCAGCAGGT GTCAACAAGA GGATGGGCCA
28001  GAGATGCAGA GCATCCACCC CAGGCCACAC AGCAGTGGCC AGAGGGTCCC
28051  AGGCCCCAGT GCTAGGCCTC TTCCTCTTCC ACTGAGGTCA CAGCTGAAGC
28101  TGGGTCAGCT CCGTGAGAGT GAGGGGTGGC GGATGTTGTA CTGACTTCCT
28151  TGGCTCAATG TGACGTCAGG GAGATTCACC CATGTTGTTG TAGAATCAGC
28201  TCAGATGCAG TGCACTGGAG GTGGATAAGC AGAATGTGGC CTGGCCGTGG
28251  GATGGGAGGG TACCCTGGAG CAGTAAGAAA GGGCCGTTAG TCACCTGAAA
28301  AATACGCTTA CAGAGACTCA GGTGAGACCC TCATGGAGTT AGTGACACTG
28351  GCCTGGGTGG CCCACAGCTC CTTCCTGCAC ACCTTCCAGG ACTCTGGAAG
28401  GCCCTCCTTA ATCCCTTCCT GTGAACTGAC CCATCCTCAC TTCTGAGCTT
28451  TTAGTGCTTG AAACATTTAT TGTATTTTCT GCAGAGAAGC ACCTGAGGCA
28501  GGAGCCAGGG ACCCAGCCCT ACAACATCAG AGAAGACTCC ATTCTGGACC
28551  AAAAGGTTGC CCTGCTCAAG GCATAATGGG GCCACCCGTG GGCATCCACA
28601  GTTTGCAGGG TGTTCCGGAA GGTTCTTGTC ACTGTGATTG GATGCTGGAT
28651  GCCGCCTGAT AGACATGCTG GCCTGGCTGA GAAACCCCTG AGCAGGTAAC
28701  CCAGGGAAGA GAAGGAAGCC AGGCCTGGAG GTCCACGGCA GTGGGGAGTG
28751  GGGCTCACTG GCTTCCTGTG GGATGACTGG AAAATGACCT CGCTGCTGTT
28801  CCCTGGCATG ACCCTCTTTG GAAGAGTGGT TTGGAGAGAG CCTTCTAGAA
28851  TGACAGACTG TGCGAGGAAG CAGGGGCAGG GGTTTCCAGC CCGGGCTGTG
28901  CGAGGCATCC TGGGGCTGGC AGCACCTTCC CGGCTCACCA GTGCCACCTG
28951  CGGGGGAGGG ACGGGGCAGG CAGGAGTCTG GGAGGCGGGT CCGCTCCTCT
29001  TGTCTGCGGC ATCTGTGCTC TCCGAGAGAA AACCAAGGTG TGTCAAATGA
29051  CGTCAAGTCT CTATTTAAAA ATAATTTTGT GTTTTCTAAA TGGAAAAAGT
29101  GATAGCTTTG GTGATTTTGT AAAAGTCATA AATGCTTATT GTAAAAAATA
29151  CAGGAAACCA CCCCTCACCC TGTCCACTTG GGTGATCATT CCAGACCCCT
29201  CCCCAAACAT GCATATGTAC CTGTCCGTCA GTGTGTGGAT GTATGTTTAC
29251  AGTTCTACAT AAATGGGATC ATTTTATACA TGGTGCTCTG GAACCCACAT
29301  TTTTCATGCA GTCATTTGCA GTGAATTATT TATTGTGATA ATAAATAGCA
29351  TTAGAATACA AGATTTTTAA TGTCTGCGTG GTATTTTGGT CTATATATGC
29401  ATCATAATTG ACTTACCGAG CCCTCTGTTC AACGTGTGCG TGGGTTAGAG
29451  ACGGGATCGT GCCTCCTTTA GATGTGTCAG TTGAAGCCCT TGCCCTCTAT
29501  GTGACTGCGT TTGGAAACAG GGCTTTTAGG GGGTAACTAG GTTTAATGAA
29551  GGTCATAAAG GTGGGCCCTG AACCGATAGC TTTAGTGTCC TCGTGAGAAG
29601  AGACGCCAGA GAGCTCGTTC TCTGCACCCT CACACCCCAG GGAACTCCAT
29651  GAGAGGACAC GGCAAAACCA GGCCATGCGC CCACCAGGAA GAAAGGCCTC
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29701  ATGAGGACCC CAGCCTCCAA AACTGGGAGA AGATGAATCT CTGTGCTAGG
29751  CCCCGCAGCC TGGGGTGATC TGTGACGGCG GCCTGAGCAG GTGAGGACTG
29801  CCTGCATGTT TGTATTTTTA TGAATGCTTT GATTGAGTCT GGGGGTAAAT
29851  CCCTGGAGGC CTGTGGCAGC CTCAGAGGTG TGTTCTCCCT GCACTTTCTT
29901  CAAGAAGAAT GTGGCCTGCC CTGCTGAGCC TCGTTCTGCC CGTTCTGCCC
29951  GGGCAGTCCC GGCCAATGTC AGCGCAGCAA GGGGAGGGCC TCTGTAACCA
30001  GGGCTGCTGG CTGCGGGGCT CCCCACTGGA CACGGGAGCG GACATTGGAG
30051  TGTCCTTCAT CCGCGTCACT CTTCCAGGTC CCTTGCCTCC CATTTTCCTT
30101  CCTTCCTTCC TCTTTCTTTC CTTCCTTCCT TTCCTCCCTT GCTCCCTTCC
30151  TTTTCTTTCT TCCTTCCGTT TTTCTTTCCT TTCTTCCTTC CTTTCTTTTT
30201  TTCCTTCCCG TTCTCCCTTT CTTCCTCCCT CCACCCCTTT CTTCTCACTG
30251  TGTTCCCCAG GCTGGTCTTC AACTCCTGGG CTCAAGCAAT CCTCTTGCCT
30301  CAGCCTCTGG TGTGGCTGGG ACCACAGACA CATGCCACCG CGCCAGGCTA
30351  ATTTGTTAAT TTTTTTTATA GAGACAGGGT CTCACTTTGT TTCCCAGGCT
30401  CGTCTCAAAC TCCTGGGCTC AAGTGATACT CCAGCTTCAG CCTGAAGTGC
30451  TGGAATTAAG GTGTGAGCCA CCATGCCTGG CCCTCTCTCA TTCACAAGTG
30501  AACCGTTCAC CCCTGCCCTC CAATCCATGT CGTTTCTGAC CTCAGGCAGC
30551  TTCTCTTTCT ACATAAAGTG AACCTGTCCC AAAGCTGTGC TCACTGGGCC
30601  CCCCTGCCAG GGCTGGAAGA GGCAGCAGTT CACATTTGGC TTGCACTCAC
30651  ATACCAAGGG CATCCATGCT TGAACCTAGA CATGGTTCAT TCACAGGGAT
30701  GGGTGAAGGT AAACAGACTG TGGCGGGCAC TAGGCACTAT CAGTTTCATA
30751  AATCTGCATA CCACCTGTGA CTCAGCAGTT ATGCTTCTCG GAATCTACTC
30801  AAACATGCTT GAGTCAGCCT TCCAGGAAGC AGGCACAAGG ACGTTTGTGA
30851  CAACTTGGTC AGTAATTTTA AGAAGTAGGA AGAAACCTGA GTTTCTCTGA
30901  ATTCGGTAAC ATCTTGACTG TAGGACACAC GAATAATGCC GTGGAATATT
30951  GTGCAGCAGT TAAAAGAAAT GAGGTGAAGG CCGGGTGTGG CAGCTCACGC
31001  CTGTTATCTC AGCACTTTGG GAGGCCGAGG CTGGTGGATC ACTTAAGGTC
31051  AGGAGTTTGA GACCAGTCTG GCCAACATGG CGAAACCCTG TCTCTACTAA
31101  AAATACAAAA ATTAGCTGAC CTCTGTGACA GAGTGAGACT CTGCCTCAAA
31151  AAAAAAAAAA AAAAAAAAAA AAAAATGAGG TGAAGCTTTA AGTTGTAACA
31201  CTGATTTTGG GGTGCAATAA AGCAAGTTGC AGAATGATAC CCATGTTAAG
31251  ATGCTATTTG AGTGAACACA CGGACCAAAC AATTCTATGT TGGGTACAAA
31301  TTTAAGAAAG AGTTCTGGGC TGGGCACGGT GGCTCACAAC TGTAATCCCA
31351  GCACTCTGGG AGGGTGAGTC GGATGGATCA GGAGGTCAGG ACTTCTAGAC
31401  TAGCCTGGCC AATATGGTGA AACCCCATCT CTACTAAAAA TACAAAAATT
31451  AGCCAGGCGT GTTGGCGCGT GTCTGGAGTC CCAGCTACTC AGGAGACTAA
31501  GGTAGGAGAA TCACTTGAAC CCGGGAGGCA GAGGTTGCAG TGAGCTGAGA
31551  TCATGCCACT GCACTCTGGC CTGGGCAACA GAGCGAGACT CAAAAAATAA
31601  ATAAATAAAT AAATAAAATA AATAAGAGTT TTCTGCACTT TGGGAGGCCT
31651  GTAGTCCCAG CTACTCTGGA GGCTGAGGCA AGAGGATCAC TTGAGCCTGG
31701  GGGGGTCGAG GCTGCAGTGA GTCCTGATTG TGTCACTGAA ATCCAGCCTG
31751  GGCAACAGAG TGAGAC (SEQ ID NO:5)
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FEATURES:

Start:	914
Exon:	914-1147
Intron:	1148-2008
Exon:	2009-2286
Intron:	2287-2517
Exon:	2518-2563
Intron:	2564-5066
Exon:	5067-5146
Intron:	5147-7047
Exon:	7048-7190
Intron:	7191-15250
Exon:	15251-15426
Intron:	15427-15844
Exon:	15845-15917
Intron:	15918-18499
Exon:	18500-18550
Intron:	18551-20881
Exon:	20882-20942
Intron:	20943-21839
Exon:	21840-21895
Intron:	21896-22194
Exon:	22195-22335

Intron:	22336-23816
Exon:	23817-23944
Intron:	23945-24261
Exon:	24262-24361
Intron:	24362-24840
Exon:	24841-24974
Intron:	24975-27018
Exon:	27019-27091
Intron:	27092-28484
Exon:	28485-28576
Stop:	28574

CHROMOSOME MAP POSITION:

#	SHGCNAME	CHROM#	LOD_SCORE	DIST.(cRs)
1	SHGC-56719	17	15.9	14
2	SHGC-58932	17	15.68	14
3	SHGC-97	17	14.5	17
4	SHGC-53147	17	13.3	22
5	SHGC-33067	17	12.52	23

ALLELIC VARIANTS (SNPs):

POSITION	Major	Minor	Context
30344	g	a	aagcaatcctcttgcctcagcctctggtgtggctgggaccacagacacat [g/a]ccaccgcgccaggctaatttgttaatttttttttatagagacagggtctca
31170	a	g	ctctgtgacagagtgagactctgcctcaaaaaaaaaaaaaaaaaaaaaaa [a/g]aaaatgaggtgaagctttaagttgtaacactgattttggggtgcaataaa
16256	c	t	aaacgctgctgtctgattttaaggtaacgtcactgaaaggggagtttgca [c/t]atggagctgggttgagatctgcatgaacaatcatattctatggtgtctcc
13376	a	t	catgcccagctaatttttgtatttttagtaaagacagagcttcactgtgt [a/t]ggctgggccagtctcgaattcctgacttcaggtgattcagctgcctcggc
12210	t	c	atgttgggattacaggtgtgagccactactcctggtcttctttcaacttt [t/c]gacttttgtatgtctgaaagtctattttgccttcatttttcaaagatagt
12072	g	c	catgcatcaccacgcctggataatttttttatttttacttttttgtagagat [g/c]gtgtcttcctacgttgcccaggctggtctcttactcctgggctcaaggga
11922	g	t	taactctttcagcatttttttttttttttttatttgacaggattcactct[g/t]tcactcaggctggaatgcagtggtacaattatagttcactgcagccttga
11903	-	a	ttgcaggcctgttggtgattaactctttcagcatttttttttttttttt[-/a]tttgacaggattcactctgtcactcaggctggaatgcagtggtacaatta
10009	c	g	ctttgacctgtggattatttagaagtggattatatgatttcttctgtgaa [c/g]catgggagttatttagtttccaaatagttgggggtttcccaattagtact
4519	c	t	cctgcccaggacctcagagctggtatcgtggtgggaggctcctactttgc [c/t]gaggattccccaagctggtttcttgaagcccctcagagccctccacatct
4181	a	g	aacagtcccagagtccgccccccaggatgtcctaaccccacccaccctgt [a/g]cgcagcagttttagggcagggtccttgagcctgtggccatgggatccagg

20952	a	c	tccctcgtctcctcctacccggtcacaggcagctttggacggtgagtgac [a/c]tgtccgcctcttctgtttgcccacgttggacgccttaacgttgttacgct
20987	t	c	tggacggtgagtgacatgtccgcctcttctgtttgcccacgttggacgcc [t/c]taacgttgttacgctgacaaggagtctgcctgccctgaccccggcgcccc
21620	g	a	ccccacctggatgggggcaggagacagagtcggcaggaacctgaaaggac [g/a]cgtgcttcctgagcttcttcctatagtcagggtggcccaagcgcggctgt
21795	t	c	ctgacgtcccctcggaagatcagccacaggagtgtggactgaggtctccc [t/c]tttcccggcccctggtgactgacggtctctgtgttgccttccaggacagc
22753	a	t	agcggaacagccttgcaccctggctcagaatggcagttccttttttttttt [a/t]ttattattatttttatttttttttattgatcattcttgggtgtttcttgc
22945	g	a	gcagaacaaaatgaaaagtctcccatgtctacttctttctacacagacac [g/a]gcaaccatccgatttctcaatcttttccccacctttcccccctttctatt
23032	g	a	ccccccttttctattccacaaaaccgccattgtcatcatggcgcgttctca [g/a]tgagctgttgggtacacctcccagacggggtggtggccgggcagaggggc
23738	g	a	ggggctgcttggggtccatgagcacctttactcatatgtgggggggcagaa [g/a]gctgtcccgctggtcagcagggccatgttggggcctcgggcagctgccgg
23952	t	g	tctgctcatgctcctgcactctgcagccaggcctgagaccaaggtacccc [t/g]ccgtggcctctgagtggggagtgtgctgggggcaggattcctgggcatgg
24123	a	g	gggcagtcaccttgctataaaccatggtgttctcccactgtgtgggggcc [a/g]tgggggtctccccttagcacccctctcccggtcccctgcagcacgctagg
24527	c	-	caggcatctctgagtgggctggaccgtcctctgtgggcctcagccagtgg [c/-]tgctgcagcaagggtggtggctccccacatatcactccttccctgcccct
24691	c	t	agggaaacagctgctgctgtcaccaaacaattgtctctggtcctgccacc [c/t]gaatcccccaactgggcgactcagccgccacgagatggagcactctggcc
25015	g	a	gggcctgcaggtgggtgtgcactgggatgccttaggggttagcagctgcc [g/a]gaaggccttcctgtgcctgcctcccatggcgaatgtgacatctctgggct
25191	g	t	ctcgtccctccctgtggaaggggagcggtggcccccagccctccgaggg [g/t]tcacgttatggcttctggtcactgccacactgtcctttgtgctggggaca

POSITION	Major	Minor	
30344	g	a	Intron
31170	a	g	Intron

16256	c	t	Intron
13376	a	t	Intron
12210	t	c	Intron
12072	g	c	Intron
11922	g	t	Intron
11903	-	a	Intron
10009	c	g	Intron
4519	c	t	Intron
4181	a	g	Intron
20952	a	c	Intron
20987	t	c	Intron
21620	g	a	Intron
21795	t	c	Intron
22753	a	t	Intron
22945	g	a	Intron
23032	g	a	Intron
23738	g	a	Intron
23952	t	g	Intron

24123	a	g	Intron
24527	c	-	Intron
24691	c	t	Intron
25015	g	a	Intron
25191	g	t	Intron

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Gene structure of Splice Form 2:
protein      1 MPSSVTALGQARSSGPGMAPSACCCSPAALQRRLPILAWLPSYSLQWLK
               MPSSVTALGQARSSGPGMAPSACCCSPAALQRRLPILAWLPSYSLQWLK
               MPSSVTALGQARSSGPGMAPSACCCSPAALQRRLPILAWLPSYSLQWLK
genomic    687 acttgagcgcgattgcgagcagttttcggccaaccacgtccattcctca
               tccctcctgacgccgcgtccgcgggcccctaggtcttcgtcgactagta
               gttgggggtgcgctccggcgcccccctgcgggggccgggggccccgggggg


protein     50 MDFVAGLSVGLTAIPQALAYAEVAGLPPQ
               MDFVAGLSVGLTAIPQALAYAEVAGLPPQ
               MDFVAGLSVGLTAIPQALAYAEVAGLPPQ
genomic    834 agtgggctggcagaccgcgtgggggccccGTGAGGC  Intron 1
               tattcgtctgtcctcactcacatcgtcca<0-----[921  : 1781]
               gtcccccatcctctcgggcttagtacgcg


protein     79    YGLYSAFMGCFVYFFLGTSRDVTLGPTAIMSLLVSFYTFHEPAYAV
                  YGLYSAFMGCFVYFFLGTSRDVTLGPTAIMSLLVSFYTFHEPAYAV
                  YGLYSAFMGCFVYFFLGTSRDVTLGPTAIMSLLVSFYTFHEPAYAV
genomic   1779 CAGtgcttgtagttgtttcgatcggacgcagaatccgtttatcgcgtgg
               -0>agtaccttggttatttgccgatctgcccttctttctactaaccact
                  tccctccgcccgtccgcccgtgtgcccctgccgcccccctgccctg


protein    125 LLAFLSGCIQLAMGVLRLAHISPHPLGLGGAGTSSMSPLGWPGFLLDFI
               LLAFLSGCIQLAMGVLRL    P   G           L     L  F
               LLAFLSGCIQLAMGVLRLGEALPSCQG---------DALDLSICLFAFQ
genomic   1920 ccgtctgtaccgaggcctgggccttcg         ggcgcaatttgtc
               ttcttcggtatctgttgtgactccgag         actatgtgttcta
               ggccgccccggcggcgtgtgtattcag         tccccctcgtata


protein    174 SYPVIK                              FTSAAAVTIGFGQIK
                YP ++                              FTSAAAVTIGFGQIK
               VYPRVR           G:V[gtc]           FTSAAAVTIGFGQIK
genomic   2040 gtccgcGTGTGTGCG  Intron 2   AAGCtatggggaagtgcaa
               tacgtg  <2-----[2060 : 2347]-2> tccccctctgtgata
               ctctgt                             cctttccccctagcg


protein    196                          NLLGLQNIPRPFFLQVYHTFLRIAET
                                        NLLGLQNIPRPFFLQVYHTFLRIAET
                                        NLLGLQNIPRPFFLQVYHTFLRIAET
genomic   2394 GTAGGCA  Intron 3   CAGaccgccaacacttccgtcatcaagga
               <0-----[2394 : 4901]-0>attgtaatcgctttataacttgtcac
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                                        cggaagcccggccgggcccccgtagc

protein    222                                  VGDAVLGLVCMLLLLVLKLMRDH
                                                VGDAVLGLVCMLLLLVLKLMRDH
                              R:R[agg]          VGDAVLGLVCMLLLLVLKLMRDH
genomic   4980 AGGTACCCC  Intron 4   CAGGgggggcgcgtaccccgcacacgc
                 <2-----[4982 : 6882]-2> tgacttgttgttttttattgaa
                                                atcccgggccgggggggggggcc

protein    246 VPPVHPEMPPGVRLSRGLVWAATT
               VPPVHPEMPPGVRLSRGLVWAATT
               VPPVHPEMPPGVRLSRGLVWAATT                A:A[gct]
genomic   6953 gccgccgaccggccacgcgtggaaGGTGAGGG  Intron 5
               tcctacatccgtgtgggttgcccc <1-----[7026 :10803]
               gtccccggcttggcctggcgtcga

protein    270       RNALVVSFAALVAYSFEVTGYQPFILTGETAEGLPPVRIPPFSV
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NUCLEIC ACID MOLECULES ENCODING HUMAN TRANSPORTER PROTEINS,
AND USES THEREOF

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